



## King's Research Portal

DOI:

[10.1038/s41572-019-0138-4](https://doi.org/10.1038/s41572-019-0138-4)

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Lord, C., Brugha, T. S., Charman, T., Cusack, J., Dumas, G., Frazier, T., Jones, E. J. H., Jones, R. M., Pickles, A., State, M. W., Taylor, J. L., & Veenstra-VanderWeele, J. (2020). Autism spectrum disorder. *Nature Review Disease Primers*, 6(1), [5]. <https://doi.org/10.1038/s41572-019-0138-4>

### Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### Take down policy

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

# **Autism spectrum disorder doi:10.1038/s41572-019-0138-4 <https://rdcu.be/b0nzi>**

Catherine Lord<sup>1</sup>, Traolach S. Brugha<sup>2</sup>, Tony Charman<sup>3</sup>, James Cusack<sup>4</sup>, Guillaume Dumas<sup>5</sup>, Thomas Frazier<sup>6</sup>, Emily J. H. Jones<sup>7</sup>, Rebecca M. Jones<sup>8,9</sup>, Andrew Pickles<sup>3</sup>, Matthew W. State<sup>10</sup>, Julie Lounds Taylor<sup>11</sup> and Jeremy Veenstra-VanderWeele<sup>12</sup>

1 Departments of Psychiatry and School of Education, University of California, Los Angeles, Los Angeles, CA, USA.

2 Department of Health Sciences, University of Leicester, Leicester, UK

3 Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK.

4 Autistica, London, UK.

5 Institut Pasteur, UMR3571 CNRS, Université de Paris, Paris, France.

6 Autism Speaks, New York, NY, USA.

7 Centre for Brain & Cognitive Development, University of London, London, UK.

8 The Sackler Institute for Developmental Psychobiology, New York, NY, USA

9 The Center for Autism and the Developing Brain, White Plains, NY, USA.

10 Department of Psychiatry, Langley Porter Psychiatric Institute and Weill Institute for Neurosciences, University of California, San Francisco, CA, USA.

11 Department of Pediatrics and Vanderbilt Kennedy Center, Vanderbilt University Medical Center, Nashville, TN, USA.

12 Department of Psychiatry, Columbia University, New York, NY, USA.

## **Acknowledgements**

The authors thank James McCauley, Sandra Gaspar, Katherine Byrne, and Alison Holbrook from UCLA for help with manuscript preparation. Dr. Samul Tromans is thanked for his updated review of the epidemiology literature. We recognize the many investigators who contributed research that we cannot cite due to space limits. C.L. is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD; R01 HD081199), the National Institute of Mental Health (NIMH; R01MH081873-01A1) and the Simons Foundation. T.S.B. is supported by grants from the Health and Social Care Information Centre, Leeds, and the National Institute for Health Research (NIHR HTA [Grant ref NIHR127337]). T.C. is supported by grants from Innovative Medicines Initiative 2 (No 777394), the Medical Research Council (MRC; grants MR/K021389/1), and the NIHR (grant 13/119/18). J.C. is funded by Autistica. G.D. is supported by the Institut Pasteur. T.F. is supported by the Autism Speaks Foundation. E.J. is supported by grants from the Economic and Social Research Council (ESRC; ES/R009368/1), the Innovative Medicines Initiative 2 (No 777394) and the MRC (MR/K021389/1)the Simons Foundation (609081). R.J. would like to acknowledge the Mortimer D. Sackler Family and the NIMH: R01MH114999. J.L.T. is supported by grants from the FAR fund and the National Institutes of Mental Health (R34 MH104428, R03 MH 112783, R01 MH116058). A.P. is partially supported by Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London and NIHR NF-SI-0617-10120. M.S. is supported by the National Institute of Health (NIH, MH106934, MH109901, MH110928, MH116487 MH102342, MH111662, MH105575, MH115747), the Overlook International Foundation and the Simons Foundation. J.V.W. is supported by the Mortimer D. Sackler, M.D., Foundation, the National Institute of Health (NIH; MH016434, MH094604) and the New York State Psychiatric Institute. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

44

## 45 **Author Contributions**

46 All authors read and edited the full document. Introduction (C.L.), Epidemiology (T.S.B.),  
 47 Mechanisms/pathophysiology (M.W.S., G.D., R.M.J., T.C. and E.J.); Diagnosis, screening and prevention  
 48 (T.C., E.J. and T.S.B.), Management (T.S.B., T.C., E.J., J.L.T. and J.V.W.), Quality of life (J.L.T., J.C. and T.F.),  
 49 Outlook (C.L. and A.P.); Overview of Primer (C.L.).

50

## 51 **Competing Interests**

52 C.L. acknowledges the receipt of royalties from Western Psychological Services for the sale of the Autism  
 53 Diagnostic Interview-Revised (ADIR), the Autism Diagnostic Observation Schedule (ADOS) and the Social  
 54 Communication Questionnaire (SCQ). T.S.B. has received royalties from Cambridge University Press and  
 55 Oxford University Press. T.C. has served as a consultant to F. Hoffmann-La Roche Ltd and has received  
 56 royalties from and Guilford Publications and Sage Publications. T.F. has received federal funding  
 57 research support from, acted as a consultant to, received travel support from, and/or received a  
 58 speaker's honorarium from the Brain and Behavior Research Foundation, Bristol-Myers Squibb, the Cole  
 59 Family Research Fund, Ecoeos, Forest Laboratories, Ingalls Foundation, IntegraGen, Kugona LLC,  
 60 National Institutes of Health, Roche Pharma, Shire Development and the Simons Foundation. J.L.T.  
 61 receives compensation from Sage Publishers for editorial work. A.P. receives royalties from Imperial  
 62 College Press, Oxford University Press Western Psychological Services. M.S. serves on the scientific  
 63 advisory boards and has stock or stock options for ARet Pharmaceuticals and BlackThorn Therapeutics.  
 64 J.V.W. has consulted or served on an advisory board for Novartis, Roche Pharmaceuticals and SynapDx,  
 65 has received research funding from Forest, Novartis, Roche Pharmaceuticals, Seaside Therapeutics,  
 66 SynapDx, and, and has received an editorial stipend from Springer and Wiley. J.C., E.J., R.J., G.D. declare  
 67 no competing interests.

68

## 69 **Abstract**

70 Autism Spectrum Disorder (ASD) is a construct used to describe individuals with a specific combination  
 71 of impairments in social communication and repetitive behaviours, highly restricted interests and/or  
 72 sensory behaviours beginning early in life. The worldwide prevalence of ASD is just under 1%, but  
 73 estimates are higher in high-resource countries. Although gross brain pathology is not characteristic of  
 74 ASD, subtle anatomical and functional differences have been observed in postmortem, neuroimaging  
 75 and electrophysiological studies. Initially it was hoped that accurate measurement of behavioural  
 76 phenotypes would lead to specific genetic subtypes, but genetic findings have mainly applied to  
 77 heterogeneous groups that are not specific to ASD. Psychosocial interventions in children can improve  
 78 specific behaviours, such as joint attention, language and social engagement that may affect further  
 79 development and could reduce symptom severity. However, further research is necessary to identify the  
 80 long-term needs and treatments and the mechanisms behind them that could result in improved  
 81 independence and quality of life over time. Families are often the major source of support for people

with ASD throughout much of life and need to be considered, along with the perspectives of autistic persons, in both research and practice.

## [H1] Introduction

Autism spectrum disorder (ASD) is a common, highly heritable and heterogeneous neurodevelopmental disorder that has underlying cognitive features and commonly co-occurs with other conditions. The behaviours, strengths and challenges of people with autism, or ASD, have attracted the attention of scientists and clinicians for at least 500 years (Fig. 1). ASD is a heterogeneous disorder and, reflecting this heterogeneity, the term autism has been used in various ways to describe both a broader presentation, and then a specific diagnosis when it was considered to be one subgroup within the general diagnostic category of ‘pervasive developmental disorders’ (PDDs), a group of disorders that was introduced in Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM III) in 1980 to convey the idea of a broader spectrum of social communication deficits. Owing to of lack of clear borders between the PDDs and difficulties in reliably distinguishing them, the current diagnostic systems, the International Classification of Diseases 11th Revision (ICD-11) and the DSM-5 use the umbrella term ‘ASD’, and differentiate individuals using additional clinical specifiers and modifiers.

Manifestations of ASD include impairments in social communication and interaction, sensory anomalies, repetitive behaviours and varying levels of intellectual disability (Table 1). Together with these core symptoms, co-occurring psychiatric or neurological disorders are common in people with ASD, of which, hyperactivity and attention disorders (such as attention-deficit/hyperactivity disorder (ADHD)), anxiety, depression and epilepsy are fairly prevalent. A diagnosis of ASD is reached after obtaining a detailed developmental history, often from the parents, and observation of the individual interacting with parents or other individuals<sup>1,2</sup>. Early intervention for children with ASD is key owing to common difficulties in communication. The types of interventions used change throughout life and include parent-mediated interventions and/or therapist-delivered interventions in childhood, school-based strategies and techniques to promote independence in adulthood. Pharmacological therapies can be used to treat some of the associated symptoms of ASD, such as irritability, and comorbidities, such as anxiety.

This Primer discusses the epidemiology and mechanisms of ASD, together with the diagnosis and treatment of people with this condition. Three themes are addressed: mechanisms of causality and change over time, heterogeneity within and between individuals with ASD, and outcomes across the lifespan.

## [H1] Epidemiology

[H2] Prevalence [Au: subheading introduced for flow, OK?YES]

Epidemiological administrative and community-based [Au:OK?YES] studies have suggested that ASD is more common in males than in females, with reported ratios [Au:OK to add ‘with reported ratios’ here?] ranging from 2.1–5. 1, with an estimate of 4.1 in the 2010 [Au:OK?] Global Burden of Disease study<sup>3,4</sup>. The sex ratio is slightly lower in studies that use population-wide testing [Au: I’ve edited ‘screening’ to ‘population-wide testing’ here based on this comment. Do we need to edit the text in the Diagnosis, screening and prevention section too?] to find community cases within a population compared with the

more common passive case-finding studies that review administrative data (for example, medical or special educational records), and that may result in less plausible associations and, therefore, artificially increase prevalence estimates<sup>5</sup>. Active case-finding that does not rely on administrative records has demonstrated an equivalent community rate of ASD in men and women with moderate to profound intellectual disability<sup>4</sup>. Thus, even the most widely accepted tenet of our understanding of factors associated with ASD is far from straightforward.

Estimates of the prevalence of ASD in various populations and settings differ according to the method of ascertainment used in the study, including definition, sampling and the extent of independent population case assessment. Of note, the Global Burden of Disease study uses all known data from administrative and community survey sources on a disease or disorder to model associations (particularly with time) to examine trends. In the 2010 GBD study [Au:OK?] , an estimated 52 million people had ASD globally, equating to a prevalence of 1 in 132 individuals<sup>6</sup>. Worldwide, little interpretable variation in the prevalence of ASD between regions or ethnicities has been reported [Peer reviewer comment: It would be useful to add a few comments about prevalence estimates around the world and how they differ based upon resources of the countries (i.e., are likely not due to regional variations in prevalence or differing environmental conditions, but instead reflect access to services). This could enhance the paper's global perspective. [Au: could we quote additional data from the GBD study here? If these data are lacking I would mention this here so it's clear to readers]. Indeed, one systematic review did not find a strong effect of ethnic, cultural or socioeconomic factors on the prevalence of autism [Au:OK]<sup>7</sup>. However, statistical power to detect any effects was limited in the available data sets, particularly in low-income countries. An increased prevalence of ASD has been reported in migrant groups in some studies<sup>8</sup> with few clear factors that might contribute to a greater prevalence in an Afro-Caribbean population in higher income countries<sup>9,10,11</sup> in the absence of any evidence of geographical variation<sup>7</sup>. However, a survey of adults in the general population has shown that rates of ASD in black and minority ethnic groups may be lower than in the rest of the population<sup>12</sup>; data from indigenous and Aboriginal cultures are very limited.

Many individuals and groups presume that autism rates are increasing over time, but this supposition is based on data from administrative records rather community-based studies. Indeed, after accounting for methodological variations between studies, there was no clear evidence of a change in the prevalence of ASD in the community between 1990 and 2010<sup>13</sup>. In addition, general population and systematic case-finding community-based [Au:OK?] surveys (including testing of representative populations) have also confirm the lack of significant change in prevalence rates in childhood<sup>14</sup> and adulthood<sup>15</sup> over time. No significant evidence is available supporting that ASD is rarer in older people, which provides further evidence against the suggestion that ASD is increasing in prevalence over time<sup>4</sup>. Even in high-income countries with strong ASD public health policies, there is evidence that ASD in adults goes largely unrecognized, whereas administratively recorded diagnoses in children increase year by year<sup>16</sup>. This finding highlights the importance of obtaining information on ASD rates in settings where professionals may be able to improve its recognition. The prevalence of ASD in mental health inpatient settings is estimated to be far higher than in the general population, ranging from 4–9.9%<sup>17</sup>.

## [H2] Environmental factors

One review of systematic reviews and meta-analyses of environmental risk factors for ASD included a comprehensive coverage of the literature, a discussion of the limitations of research and the need for long-term prospective cohort-based studies to begin to address these limitations<sup>18</sup> (Fig. 2). This and other studies identified environmental risk factors for ASD as advanced parental age<sup>19</sup> and birth trauma, particularly if due to proxies of hypoxia<sup>18</sup>. Moreover, maternal obesity, a short interval between pregnancies, gestational diabetes mellitus and valproate use during pregnancy have all been associated with increased risk of ASD [Au:OK?] (Fig. 2). However, it should be noted that these factors cannot be considered causal, but could be reactive, independent or contributory for ASD. Studies evaluating risk factors for ASD that have reported an absence of association are equally, if not more important, to note, including clear evidence that ASD is not associated with vaccination<sup>20</sup>. Other negative associations include prolonged labour, delivery by caesarian section or assisted vaginal delivery, premature rupture of membranes and the use of assisted reproductive technologies, among other factors (Fig. 2). Environmental risk factors could underlie risk of ASD through several complex underlying mechanisms, such as [Au: edits to improve narrative flow ok?] genetic and epigenetic related effects (see Mechanisms/pathophysiology, below), inflammation and oxidative stress, hypoxic and ischemic damage<sup>18</sup>.

## [H1] Mechanisms/pathophysiology

Many cognitive theories have been suggested to underlie the behavioural and developmental manifestations of ASD, although the prominence and the consensus on the potential explanatory value of these theories have declined in the past decade. These theories range from ‘social first’ theories, such as the theory of mind (or mentalizing) and social motivational deficit theories, to global processing deficit theories including attentional control, executive dysfunction and weak central coherence or enhanced perceptual processing theories<sup>21,22</sup>. Although many of these theories had a useful descriptive role and provide potential insights into differences in how autistic individuals might process and experience the world around them, the theories pertain to neurodevelopmental disorders in general and lack specificity for ASD), largely non-developmental, applying only to a single point in time, and lack evidence as explanatory models. Nevertheless, they have been useful in clinical practice and underlie some recently proposed interventions, such as CBT-oriented treatments for anxiety<sup>23</sup>.

Following cohorts of infants from gestation or birth to 2 or 3 years of age (that is, when a diagnosis of ASD can be established) enables the study of the brain and behavioural manifestations of ASD as they emerge<sup>24</sup>. Indeed, prospective studies of infants with a relative with ASD have yielded a number of insights into the mechanisms of this disorder. For example, infants who develop ASD later in childhood have substantially typical profiles of interest in faces<sup>25</sup> and eyes<sup>26</sup> at 6 months of age, which have cast doubt on social orienting theories in which ASD originates from a primary deficit in innate patterns of subcortically-mediated social orienting<sup>27</sup>. In addition, subtle but diffuse differences in encephalography (EEG) and in other measures of brain function have been demonstrated in autistic people (see ‘Findings from electrophysiological studies’, below), which could represent alternative pathways to a common end-state phenotype or to whole-brain alterations in synaptic signalling pathways that have effects on development [Au: edits for brevity ok?]<sup>28</sup>. Such considerations highlight the limitations of deterministic models of ASD, in which a genetic change leads to a synaptic change that relates to a canonical symptom<sup>29</sup>. Rather, there

is likely a complex set of developmental interactions, in which the child's emerging brain activity and behaviour have bidirectional relationships to synaptic signalling and gene expression<sup>30</sup>.

## [H2] Genetics

Twin and family studies consistently demonstrate that ASD has a particularly large genetic contribution, with estimated heritability ranging from ~40 to 90%<sup>31,32</sup>. In addition, one analyses demonstrated that ASD is among the most heritable common medical conditions<sup>33</sup>. More than 100 genes and genomic regions have now been confidently associated with ASD<sup>34,35</sup>, mostly based on the study of heterozygous, germ-line, *de novo* mutations. These genetic changes range in size from a single base (or nucleotide)<sup>36–38</sup> to submicroscopic segments of DNA of thousands to millions of bases (also known as copy number variations (CNVs))<sup>39,40</sup>. Whether these genetic changes lead to alterations in the sequence of DNA or the structure of the chromosome, changes that have a functional effect on protein-coding regions of the genome have the strongest and most reliable association with ASD risk. Collectively, these *de novo* heterozygous mutations are rare and confer relatively large risks of ASD<sup>41</sup>. With genetic studies now including cohorts of up to tens of thousands of individuals and the associated increase in statistical power, common, transmitted alleles of modest effect size, mostly corresponding to the non-coding regions of the genome, have begun to be identified<sup>42</sup>.

Studies of the genetics of ASD contrast broadly with studies of adult-onset psychiatric disorders, in which most successful gene discovery has emerged from genome-wide association studies (GWAS), which assess common alleles of small effect size. Indeed, the earliest successes in ASD presaged a more general finding that the contribution of rare, *de novo* mutations in coding regions of the genome is relatively greater among a range of early-onset disorders<sup>43–45</sup> than for typically later-onset common conditions such as schizophrenia and bipolar disorder, although there is also a surprising degree of overlap in genetic risk for overtly disparate neuropsychiatric phenotypes that remains to be further elucidated<sup>31</sup>.

The extent to which rare, high effect size mutations account for ASD risk raises some important definitional issues. Considering the overall population, the contribution of *de novo* mutations to ASD risk is quite small (~3%)<sup>32</sup>. Indeed, the vast majority of individuals who harbour genetic risk for a common condition, particularly those with variants of small effect size, will never develop symptoms or need clinical attention. By contrast, there is a marked enrichment of individuals with rare and *de novo* mutations in the clinical ASD population. Conservative estimates are that 10–20% of people with ASD harbour a *de novo* rare point mutation or CNV contributing to their presentation (34, 49,50). If the clinical population is constrained to those with ASD who are female or who have intellectual disability, multiple unaffected siblings or seizures, ~20-30% have a rare *de novo* mutation [Au: edits for clarity based on Matt's comment, ok?]<sup>34</sup>. For example, the yield of *de novo* structural and sequence variations contributing to ASD is nearly double in girls than in boys (34).

However, irrespective of the precise proportion of risk conveyed by these mutations, their most substantial contribution to the understanding of ASD is likely to be in elaborating the mechanisms of this disorder<sup>48,49</sup>. In ASD, a single *de novo* germ-line heterozygous loss-of-function point mutation can convey more risk than the cumulative effect of the top decile of polygenic risk for schizophrenia<sup>47,50</sup>. Unfortunately, although manifestly more tractable than modelling hundreds of alleles simultaneously,



addressing a single ASD mutation at a time is not synonymous with an easy avenue to clinical care of most people with ASD.

**[H3] Molecular pathophysiology.** Over the past decade there have been many studies using model systems to recapitulate so-called single gene (or monogenic) versions of ASD, such as fragile X syndrome and tuberous sclerosis complex – which cumulatively are estimated to account for <10% of clinical cases of ASD<sup>51</sup>. In addition, more recent studies have modelled the effects of rare and *de novo* mutations identified in idiopathic ASD. This literature is far too vast to review comprehensively here<sup>52,53</sup>. Although the study of ASD risk genes in model systems has revealed a great deal about general biology, how these findings relate to the pathophysiology of ASD is less clear<sup>48,49</sup>. In general, ASD risk genes tend to have a role in multiple functions in many brain regions that unfold in a spatiotemporally defined manner across development. Consequently, although manipulation of a single risk gene in a model system may lead to interesting phenotypes—including social-behavioural phenotypes in evolutionarily distant organisms—it does not necessarily illuminate its contribution to human social disability. Moreover, although a single mutation can confer a several fold increase in the risk of ASD, these variants do not demonstrate the type of causal clarity that is associated with classic monogenic neurodevelopmental disorders, such as fragile X syndrome, Angelman syndrome, Rett syndrome or tuberous sclerosis complex. In addition, the well-established sexual dimorphism of social disability adds yet another dimension to the expansive search space that exists between risk gene and human behaviour<sup>48</sup>. The challenges of disentangling the spatiotemporal dynamics of risk gene expression and protein function are made even more difficult by the reality that these may play out differently in males versus females.

Owing to these challenges, multiple approaches have emerged focusing on convergence<sup>38,40,54–57</sup>, that is, searching for points of commonality across different ASD risk genes, with the reasoning that this approach could identify shared pathological mechanisms. In fact, the earliest successes in gene discovery quickly revealed important general properties that have held up well over time, including that, *prima facie*, most proteins encoded by ASD risk genes are involved either in synaptic structure and function or chromatin modification and regulation of gene expression<sup>38,46,47,58</sup> (Fig. 3). More recently, there has been an additional focus on spatiotemporal convergence and several studies have supported a nexus in mid-fetal, glutamatergic neurons during cortical development, with modestly divergent findings regarding deep<sup>56</sup> versus superficial<sup>54</sup> cortical layers. With improvements in technology, additional regions, including striatum, have also begun to emerge as points of potential risk convergence for ASD<sup>59</sup>.

The ability to constrain future experiments to examine mutations in specific risk-associated regional, cellular and developmental contexts should allow the narrowing in on relevant mechanisms. Of note, one study used single cell technologies to examine specific cell types and developmental stages using brain tissue from people with ASD<sup>60</sup>, and demonstrated changes in transcription in multiple cell types including upper-layer cortical neurons. These types of post-mortem studies ask important but somewhat broader questions from the approaches described above, such as underlying pathology and how the brain changes and responds to pathology over time. In these studies, similar to any cross-sectional study, it can be challenging to differentiate cause from effect. Consequently, the pursuit and intersection of studies that seek to define convergence early in development and those that examine subsequent molecular, cellular and circuit level changes will be critical to illuminating pathological mechanisms.



## [H2] Neurobiology

**[H3] Findings from MRI Studies.** This section does not summarize the structural or functional literature and focuses predominantly on prospective study designs. Broader coverage of the neurobiology of ASD is needed [Au: I suggest adding a sentence or two at the end of this paragraph summarizing Rebecca's comment here, so it's clear why this section of the paper focuses on prospective studies and those in infants] MRI can facilitate understanding how the brain structurally and functionally develops differently in people with ASD, although to date, MRI results in ASD are not definitive. Although neuroimaging is typically more expensive than EEG and studies are limited by issues of replication, sometimes that is related to head motion that occurred during the scan which can erode signal<sup>61</sup>, structural studies including those using diffusion tensor imaging (DTI)<sup>62</sup> and functional MRI (fMRI)<sup>63</sup> have accelerated our understanding of how altered neural circuits relate to clinical symptoms of ASD<sup>64,65</sup>. Studying circuitry in childhood that is specifically associated with the social brain (a network of brain areas involved with processing social information), including visual areas, areas of the prefrontal cortex, subcortex and areas integrating information (such as temporal parietal function and superior temporal sulcus), could also offer insight into the neural mechanisms of ASD<sup>66</sup>. In addition, MRI may facilitate understanding the heterogeneity of ASD demonstrating subgroups of individuals with specific neurobiological alterations that could account for their symptomology.

The first MRI studies of ASD focused on cerebral and cerebellar grey matter and white matter volumes in young children<sup>67,68</sup>, although these studies were limited by studying toddlers and children  $\geq 18$  months, missing the opportunity to detect biomarkers of ASD in the first year of life. More recently, longitudinal studies have obtained multiple brain MRIs of infants at high risk of developing ASD (that is, those with a sibling with ASD; known as baby sibling studies) during their first 2 years of life, and assessed these children for ASD at this age. In these studies, detectable differences in brain structure were observed at 6 months of age in the fractional anisotropy trajectories for 12 of 15 neural fibre tracts in the brain in children diagnosed with ASD at 2 years of age compared to children not diagnosed<sup>69</sup>. Furthermore, abnormal growth in the cortical surface between 6 and 12 months of age and greater brain volume between 12 and 24 months of age was seen in children who were later diagnosed with ASD, compared with those not diagnosed with ASD<sup>70</sup> (Fig. 4). In addition, white matter integrity in the genu pathway at 6 months of age predicted the presence of restricted and repetitive behaviours at 2 years of age<sup>71</sup> and computational work demonstrated that whole brain functional connectivity at 6 months of age predicted a diagnosis of ASD at 2 years of age<sup>72</sup>. Collectively, these studies suggest the presence of disrupted neural pathways before the emergence of behavioural symptoms in children with ASD, and might provide clues about the underlying neural mechanisms of ASD. Although data from MRI studies has revealed differences in neurobiology between young children diagnosed with ASD and those without<sup>73</sup>, given that replication has been particularly difficult in these studies, more work is required before MRI can be used as a reliable biomarker of ASD<sup>74</sup>.

Task-based fMRI studies investigate circuits that are responsible for core challenges in ASD (such as language production and comprehension<sup>75</sup>), and have demonstrated hyper-activation of the superior temporal gyrus and inferior frontal gyrus and hypoactivation of the bilateral middle temporal gyrus<sup>72</sup>. In addition, these studies have demonstrated challenges in processing emotions in faces and the "social brain"<sup>74</sup>, and deficits in attention<sup>75</sup>. Studies have also shown greater sensitivity to sensory information, showing increased connectivity between the anterior insula and sensorimotor areas, and the anterior

insula and amygdala, together was associated with greater sensitivity to slightly aversive sounds and tactile information<sup>76</sup>. Although this area of research has revealed similarities or differences in people with ASD compared with comparison groups, it has been limited by averaging data across many individuals, which can mask heterogeneity and differences across age groups. In addition, the work has been limited by small sample sizes and problems with replication that is likely caused by the many challenges with MRI data collection in people with ASD, such as differences in data processing, inter-subject variability and data quality<sup>76</sup>. Longitudinal imaging<sup>77</sup> as well as associating neuroimaging data with longitudinal behavioural outcomes<sup>78</sup> can address some of these limitations characterizing differences within participants.

Resting state functional connectivity MRI studies that require participants to look at a blank screen with no task demands have been used to study intrinsic connections in the human brain. Large datasets, such as the Autism Brain Imaging Data Exchange (ABIDE<sup>79</sup>), have enabled researchers to pool data to allow more highly powered studies to address known limitations of small sample sizes and many dataset have relied on resting state studies to study neural connectivity in ASD. In these studies, evidence has emerged of both hyper-connectivity and hypo-connectivity in short-range and long-range connections throughout the brain<sup>80,81</sup>. Differences in results between studies could be due to the age of the participants<sup>82</sup>, sex differences, heterogeneity, methodological concerns<sup>83</sup> or that both connectivity states exist in ASD.

In future, MRI could be well suited to categorize subgroups of ASD<sup>84</sup>, as well as parsing out commonalities and distinctions among other developmental disorders<sup>85</sup>. Using MRI to better understand differences between boys and girls on the spectrum<sup>86</sup>, such as differences in whole brain connectivity<sup>86</sup> or the social brain<sup>87</sup>, a field in its infancy, or as a marker of biological change due to treatment has growing interest<sup>88</sup>.

**[H3] Findings from electrophysiological studies.** EEG has been historically used for the diagnosis of comorbid epilepsy in people with ASD<sup>89</sup> although it can also be used to study the mechanisms of ASD. Compared with MRI, EEG is more economical, easier to use and less invasive—which is particularly important for paediatric populations—whilst granting access to brain dynamics at millisecond timescales. Magnetoencephalography (MEG), although more expensive, provides higher spatial resolution than EEG.

Since the early recordings, the first focus of quantitative EEG was to study people with ASD in task-free conditions. Pioneering studies have revealed alterations in oscillatory activity during the resting state in people with ASD, with more slow waves and less alpha waves, as well as less intra-hemispheric and inter-hemispheric asymmetry compared to people without ASD<sup>90</sup>. More recent work has demonstrated the presence of developmental trajectories as revealed through increasingly sophisticated spatio-spectral analyses, and has revealed how differences in the trajectories of EEG power in high-risk infants may represent an endophenotypes of ASD<sup>91,92</sup>.

In terms of mechanisms, other studies have started to focus on task-based modulation of cognitive function, such as low-level perceptual anomalies and action observation that relate to the ASD phenotype. One theory proposing a specific failure in ASD of the ability of the brain to ‘mirror’ observed actions of another person (thereby named the ‘broken mirror’ theory) was based on altered  $\mu$ -wave suppression in ASD<sup>93</sup> but was later questioned both theoretically<sup>94,95</sup> and empirically<sup>96,97</sup>, pointing toward a more complex picture of dysfunctional executive functions and visual attention<sup>98</sup>. Other studies, particularly those assessing event-related potentials (ERP), have demonstrated the modulation of sensory processing in people with ASD, with observed changes in sensitivities and latency<sup>99</sup>. Differences in auditory and visual

processing could have a role in the development of core features of ASD, such as language delay and difficulty in emotion recognition although this hypothesis requires further study. Although perceptual processes appear different in people with ASD, the electrophysiological underpinning is still far from clear regarding the main ERPs like the MisMatch Negativity (MMN)<sup>100</sup> or the N170<sup>101</sup>. Although data from meta-analyses have suggested smaller MMN amplitudes and delayed N170 latencies on average in people with ASD compared to typically developing controls, additional studies are required that account for the large heterogeneity of this disorder, by moving away from averaging the data to focus either on specific subgroups<sup>102</sup> or refined modelling strategies that can capture individual differences in developmental trajectories<sup>91</sup>. Although this avenue of research has not yet been fully explored, interactive tasks that encompass real-time social interaction could allow the study of brain activity in experimental contexts that are more relevant for core ASD symptoms, rather than the more passive tasks that are used in most functional imaging studies<sup>103</sup>. Experiments focusing on human-human interaction<sup>104</sup> and human-machine interaction<sup>105</sup> have been undertaken but, so far, no study has ever made explicit use of such methods to study the electrophysiology of ASD.

In a further search for mechanisms of ASD, prospective baby siblings studies have suggested that the gradual emergence of behavioural symptoms of ASD is preceded by earlier subtle alterations in the activity of regions and networks of the social brain<sup>24</sup>. For example, early work on a small group of 5–6-month-old infants who later developed ASD observed faster but less prolonged neural activation and delayed sensitization responses to faces compared with infants who did not develop ASD<sup>106</sup>, and one report demonstrated that newborns with an increased familial likelihood of ASD showed higher signal homogeneity within core social brain networks (right fusiform and left parietal cortex<sup>107</sup>). By comparison, reduced frontal power, particularly in the high-alpha band, during quiet play at 3 months of age<sup>108</sup> and cortical hyperexcitability in the right tempo-parietal region during auditory repetition of pure tones at 9–10 months of age have been found in babies at familial risk for ASD<sup>109</sup>, suggesting that atypical patterns occur in brain regions other than those involved in social processing. Such alterations could have a cascading effect on social learning and contribute to the later emergence of behavioural symptoms of ASD, although a causal link remains to be demonstrated. Replications across different research centres are needed because many of these studies had small sample sizes, different definitions of groups and varied measures and time points.

Interestingly, results from MEG and EEG studies jointly point toward two physiological mechanisms of ASD: excitation/inhibition (E/I) imbalance and alteration of large-scale functional interactions of brain systems as quantified through connectivity analysis<sup>110</sup>. An E/I imbalance is supported by results from computational modelling of how reductions in the amount of inhibition can account for the previously observed perceptual consequences of ASD<sup>111</sup> and transcranial magnetic stimulation (TMS) studies demonstrating a neurophysiological deficit in  $\gamma$ -aminobutyric acid (GABA) receptor-mediated function in people with ASD<sup>112</sup>. In parallel, decreased long-range functional connectivity has also crystallized as a consistent mechanism<sup>113</sup>. MEG studies have especially suggested a complex functional connectivity pattern in the somatosensory cortex with reductions in the feedback (top-down) direction, but increased in the feed-forward (bottom-up) direction<sup>114</sup>. Clarifying the extent to which this pattern is a methodological artifact that could result from the predominant average-brain approach, as suggested by fMRI studies, is critical<sup>115</sup>.

Beyond use to understand the pathophysiology of ASD, the scalability and accessibility of EEG suggest that this technique could be an ideal candidate for use as a brain-based biomarker. Measures from information

theory have already provided promising case-control classification<sup>116</sup>, but developing generalizable biomarkers may require a combination of multiple EEG measures supported by robust machine learning methods<sup>117</sup>. Against the background of the current reproducibility crisis that characterizes many studies<sup>118</sup>, as well as the defining heterogeneity of ASD, the next breakthrough will certainly demand large-scale collaboration between researchers and clinicians.

## **[H1] Diagnosis, screening and prevention**

Diagnosis of ASD is made on the basis of behavioural presentation. Although substantial heterogeneity exists between and within individuals across development, a set of core diagnostic features of ASD (covering social interaction, communication and flexible or sensory behaviour) can be reliably identified by trained clinicians<sup>119,120</sup>.

### **[H2] Diagnostic criteria**

The re-formulation of the diagnostic criteria for ASD in the DSM-5 (**Table 1**)<sup>121</sup>, which is similar to the criteria in ICD-11<sup>122</sup>, contains several changes from previous editions that were based on good empirical and clinical evidence<sup>123</sup>. First, the sub-classification of 'Asperger's disorder' was subsumed under the unitary term ASD as the diagnosis was inconsistently applied even by expert groups<sup>124</sup>. This change is controversial, but the evidence supporting the inclusion of Asperger's disorder as a separate condition is very weak<sup>125</sup>. The important questions are how better to consider the factors that characterize differences among autistic individuals and ensuring that these differences are measured and addressed using neurobiological and clinical research, rather than contained within very poorly defined categories of Asperger's and PDD Not Otherwise Specified (NOS) as defined in DSM-IV. In addition, some individuals with social communication problems but not restricted and repetitive behaviours who would previously have fallen into the now-removed subcategory of PDD-NOS now receive a different diagnosis of Social communication disorder, which is not yet well-validated. Although these changes have led to concerns that the DSM-5 ASD criteria are more restrictive than those in DSM-IV, many clinicians feel that the changes better reflect clinical consensus and practice. Second, the social and communication domains of the diagnostic criteria were unified to reflect the factor structure of symptomatology. Third, sensory anomalies (hypersensory and hyposensory responsiveness and sensation-seeking) in DSM-5 were included under the 'restricted, repetitive behaviours and interests' domain to reflect their pervasiveness<sup>126</sup>. Fourth, the DSM-IV criteria required symptoms to be present in the first 3 years of life, but criteria in DSM-5 recognise symptom onset occurring in the early developmental period with the caveat that symptoms might not fully manifest until social demands exceed limited capacities. This change recognizes the developmental nature of ASD, wherein for some individuals, clear manifestation of ASD might not be apparent until mid-childhood, adolescence or even adulthood. In addition, late diagnosis (that is, diagnosis beyond early childhood) can occur even in those who received intensive early monitoring<sup>127</sup>. In addition, the DSM-5 criteria supports the use of specifiers that can denote those with a dual diagnoses, such as individuals with ASD and ADHD or other psychiatric disorders, as well genetic conditions such as fragile X syndrome or down syndrome. Beyond the clinic, these changes have

implications for large-scale data pooling efforts; for considering domains of behaviour to be modelled; and for identifying shared and distinct developmental pathways to conditions like ASD and ADHD.

## [H2] Diagnosis and screening in children

The two core elements of the diagnostic process of ASD in children are a detailed developmental history that is usually obtained from parents, covering first concerns and early history to the present day, and an observation of the child's interactions with their parents and with unfamiliar adults during a combination of structured and unstructured assessments. Ideally, observations of the young person in peer-group settings such as school or nursery would also form part of the diagnostic process. Of note, in one population-based study in the UK, girls with similar levels of symptom expression to boys were less likely to receive a diagnosis of ASD from clinical services<sup>128</sup>. This finding might reflect socio-cultural factors in the application of the diagnostic criteria, greater resilience or protective factors in girls that reduce the need for clinical services at a given symptom level, or the need for the revision of instruments used to identify symptoms to more fully cover female autistic traits<sup>123</sup>

A number of structured diagnostic interviews and observational assessments for ASD exist, but only a limited number have been rigorously tested for diagnostic accuracy relative to the gold-standard of expert clinician judgement. Although these interviews and assessments have reasonably robust sensitivity, specificity and reliability (see<sup>129</sup> for a review) and are widely used in some services in communities<sup>130</sup>, there are also challenges to the widespread adoption of the best validated instruments: the Autism Diagnostic Interview–Revised (ADI-R<sup>131</sup>) and the Autism Diagnostic Observation Schedule–2nd Edition (ADOS-2<sup>119</sup>). These challenges include the cost of the instruments and training, the time required to complete them and the need for substantial training to use them reliably<sup>132</sup>. Although expert clinical judgement was previously believed to be more reliable than reliance on instrument scores alone for the diagnosis of ASD<sup>133</sup>, more recent evidence suggests this may not be true at least in toddlers and preschool children<sup>134</sup>. The need to take a global perspective on ASD is driving attempts to develop more scalable tools, but this work is currently in its infancy (Box 1)<sup>135</sup>.

The stability of a diagnosis of ASD from the preschool years to mid-childhood is relatively high<sup>1</sup>. However, although diagnostic systems currently presuppose that ASD is a lifelong condition, there is a growing recognition that ASD has a heterogeneous developmental time course<sup>136</sup>. Indeed, sub-groups of individuals with ASD and improving or worsening symptoms over time can be identified<sup>137,138</sup>. Such developmental trajectories might be a more meaningful phenotype on which to map aetiological mechanisms than a static case-control dichotomy<sup>70,139,140</sup>. Some individuals diagnosed as children have no clinically meaningful (or even detectable) impairment later in life (so-called 'optimal outcome'<sup>141,142</sup>); one critical question in identifying mechanisms is whether this profile is associated with successful effects of early intervention or is an aetiologically distinct subtype of ASD.

**[Au: please see the comment in the Epidemiology section (line 121) regarding the use of the term 'screening' - do we need to introduce some edits here? I'd be grateful if you could take a look through this and amend as needed.] [H3] Screening and early identification.** The potential for early testing to prospectively identify children with ASD at a young age has considerable interest, and several studies have evaluated the performance of parent-report instruments between 14 and 24 months of age, such as the Modified Checklist for Autism in Toddlers (M-CHAT) and the Early Screening of Autistic Traits (ESAT) **[Au:**

examples added based on Tony's comment YES fine] <sup>129,143,144</sup>. However, there are contrasting views on the strength of the evidence for universal population-wide testing<sup>145,146</sup>. Of note, research is lacking on the effectiveness of therapeutic interventions in those identified with ASD through universal screening. In addition, although it is possible to identify some children with ASD before parents or professionals have identified concerns, diagnosis is missed in many children <sup>147</sup>, and most tested cohorts have not been systematically followed up to identify later-onset ASD in children who initially tested negatively <sup>148</sup>. Screening also often identifies children with broader developmental difficulties as well as those with ASD<sup>149</sup>. In general, such instruments could be more useful for identifying possible signs and symptoms of ASD in high-risk populations, for example in young children with older siblings with ASD<sup>150</sup>, or in those referred for speech or other developmental concerns to community paediatric services<sup>151</sup>. In addition, population-wide testing may also play a part in improving awareness and recognition of the early signs and symptoms of ASD in both professionals and the general public, which alongside ongoing developmental surveillance pathways in community services, could help to bring down the age of recognition and diagnosis. These principles also apply in low-income and middle-income countries in which testing for ASD and other neurodevelopmental disabilities has only just begun to be developed<sup>149</sup>. Very little research has been devoted to cultural and ethnic differences in either child early presentation and parents' understanding or the experience of autism, which may in fact affect how screening instruments work and thus impact on parents and families as much as autistic individuals.

**[H3] Early developmental profiles.** Understanding of onset patterns of ASD has dramatically expanded over the past 10 years, through work on infants with a first degree relative with ASD, who due to the high heritability of the condition have a 20% chance of developing ASD themselves<sup>25</sup>. Symptoms of ASD have a gradual developmental onset. Indeed, although the average age of ASD diagnosis remains ~4–5 years of age<sup>152</sup>, parents typically report first concerns to health professionals at ~2 years of age <sup>153</sup>. In many individuals, symptoms emerge during the second and third year of life (although, as per the DSM-5 onset criteria above, in others, onset might not be noticed until the child reaches school-age or later) whereas in others, symptoms become apparent after a seeming period of typical development, including a period of regression or stasis. To this end, conceptualization of what has been called 'regression' prior to 2 years of age has been reconsidered <sup>154,155</sup>. Over the first two years of life, a substantial proportion of infants who later receive ASD diagnoses show gradually accumulating delays across social, communication and language domains, suggesting that 'regression' represents a spectrum ranging from frank loss of acquired skills, to a gradual erosion (or 'plateauing') of developmental potential to individuals in whom these skills never emerge <sup>156</sup>.

## **[H2] Diagnosis and screening in adults**

Information on diagnostic methods to identify ASD in adulthood is in its infancy, with little methodologically acceptable evaluation of interview methods or screening questionnaires (including self-completion questionnaires). Clinical approaches rely heavily on extending methods developed for use in childhood to adulthood. These methods tend to rely on childhood developmental data, although validation research in adult general population-wide testing suggests good specificity and sensitivity for the observationally based ADOS Module 4<sup>157</sup>. However, typically, much research has depended on the

judgment of expert clinicians and of standardized data collection on early child development that is unlikely to be obtainable for many older adults. Given that (undiagnosed) autistic adults presenting for an ASD assessment are also more likely to have co-occurring adult mental health disorders, any method of assessment must be capable of differentiating such abnormalities in symptoms and behaviour from abnormalities due to ASD. This point has led to the suggestion that clinical examination methods to identify adult psychopathology could be extended to include ASD in addition to depression, anxiety and psychosis, among other disorders<sup>158</sup>. Semi-structured adult psychopathology interviewing has been fruitful in the assessment of closely related neurodevelopmental disorders in adults, most notably ADHD<sup>159</sup>. Given that most people in the world who are autistic are adults, and as many of these individuals have not received a diagnosis of autism<sup>4,15</sup> [Au: OK to add this text in based on Traolac's comment? I've also added callouts to the relevant references here], the development and evaluation of such adult assessment approaches is an urgent research priority.

## [H2] Co-occurring disorders

In addition to the core features of ASD, co-occurring difficulties or disorders (Fig. 5) are much more widely recognized in research<sup>160,161</sup>, although they are not necessarily adequately addressed in clinical practice<sup>162</sup>. For preschool children with ASD, language delays, motor problems, epilepsy, difficulties with sleep and eating, and high levels of activity are most commonly observed<sup>163,164</sup>. By comparison, ADHD, anxiety, obsessive-compulsive disorder (OCD), intellectual disability, academic challenges, irritability and disruptive behaviours become more apparent in school-aged children<sup>165</sup>. The proportion of individuals with depressive symptoms becomes higher in adolescents and adults<sup>166</sup>, whereas other issues often remain. Moreover, growing evidence (although it is reliant on administrative case-finding data) suggests that people with ASD have premature mortality<sup>167,168</sup> and increased risk of self-harm and possibly suicide, although the mechanisms involved have yet to be elucidated. Studies using electronic health records have demonstrated that adults with ASD are more likely to be diagnosed with many physical health conditions such as immune conditions, sleep disorders and obesity, compared with adults in the general population<sup>162</sup>.

Collectively, these difficulties and disorders contribute to ASD severity<sup>169</sup> and independence and well-being at each age<sup>170</sup>. However, it is important to note, in the context of heterogeneity, that the prevalence of each of these co-occurring conditions varies considerably with the context of the sample (such as from psychiatry referrals, neurological referrals, or schools) and the methodology used (administrative, self-report or assessed), as well as with age, level of cognitive function and perhaps region<sup>161</sup>). As many of these conditions are treatable, they are very important as clinical considerations but are also more complex than sometimes conveyed. [Au: please ensure OCD is mentioned in this section as it is mentioned in management, below. Does it manifest in adults with ASD or during adolescents?] [Au: I can't see this addition! Where was it added exactly? I have added above now...]

## [H1] Management

### [H2] Early intervention



Early intervention is seen as a priority because many young children with ASD struggle to communicate and interact with others, restricting their opportunities to learn and affecting their parents who can find their child's behaviour perplexing and challenging to manage. Thus, outcomes of such interventions include changes in the individual's availability for learning and increased parent understanding. Intervention delivered in the preschool years at an age when there is increased brain plasticity might lead to additional benefit, although this theory has not yet been empirically supported.

The primary models of psychological intervention for preschool children with ASD are developmental and behavioural. Although some consensus has been reached on the interventions that have more supporting evidence (termed 'naturalistic developmental behavioural interventions'<sup>171</sup>), there is some uncertainty and disagreement about the strength of evidence for different approaches, with almost no direct comparisons of treatments or studies to assess which child should receive what treatment or treatment intensity. Indeed, clinical trials in ASD are limited by cost, time, placebo effects and limited outcome measures, and are far behind much of the other research. This gap leaves parents and practitioners at the mercy of what is available and sometimes marketed in their region. Indeed, access to early intervention services is variable in most communities, including in high-income countries, and is mostly carried out by non-specialists supervised by specially trained professionals. In low-income and middle-income countries, most children and young people with ASD — similar to those with intellectual and developmental disabilities — will not receive specialized services<sup>172</sup>, although a number of groups have begun to test community delivery of early intervention in such settings<sup>173</sup>.

Many current interventions build on the original 'Applied Behaviour Therapy'<sup>174</sup> (ABA) and have shifted to more natural, child-initiated developmentally appropriate strategies and tasks instead of dependence on repeated 'discrete trials' (known as discrete trial training, or DTT). In addition, considerable variation exists between different intervention models in terms of mode of delivery (for example, parent-mediated versus therapist-implemented), length (12-week versus 2-year programs), intensity (from a few hours a week to ~15 hours per week) and the balance between the developmental or dyadic versus behavioural components.

Lower-intensity approaches include parent-mediated interventions whereby parents are coached to become more attuned to their child's communication signals and style (which are considered an intermediate child outcome) and to facilitate more joint engagement in play and everyday activities, designed to increase social and communication skills in the child<sup>175</sup>. Some studies have demonstrated enhanced joint engagement and joint attention (which are considered important intermediate child outcomes), with these lower-intensity approaches in preschool children compared to a control group, such as the 12-week Joint Attention Symbolic Play Engagement and Regulation (JASPER) program, both when delivered by parents in the home<sup>176</sup> and by teaching assistants in school<sup>177</sup>. However, other lower-intensity, time-limited parent-mediated interventions such as Focus Playtime Intervention (FPI)<sup>178</sup> have not improved child outcomes (such as social orienting and joint attention), although some interventions have increased parental responsiveness<sup>179</sup>. A longer program (Preschool Autism Communication Trial (PACT)), which consists of fortnightly parent-therapist sessions for 6 months, then monthly sessions for another 6 months, demonstrated improvements in parent and child dyadic behaviours such as parental synchrony and child initiations when interacting with each other (those close to the intervention target) but not symptom reduction at immediate follow-up<sup>180</sup>. A subsequent 6-year follow-up to mid-childhood at age 7 to 11 years identified modest reductions in overall ASD symptoms using the ADOS over the whole course of the study that were not detectable at the immediate endpoint, suggesting that a longer-term perspective is critical in considering outcomes<sup>181</sup>.

A higher intensity, more comprehensive approach is the Early Start Denver Model (ESDM), which combines behavioural and developmental or dyadic approaches. The ESDM is delivered by therapists for ~15 hours per week, and as part of this programme, parents are trained to improve social communication and interaction with their child. A small-scale trial demonstrated improvements in child developmental and adaptive outcomes, primarily in the language and communication domains, following 2 years of ESDM compared with treatment as usual<sup>182</sup>. One larger multi-site trial found attenuated benefits with improvement in language outcomes at two of the three trial sites, but no differences between the treatment as usual and ESDM groups in overall developmental ability, adaptive behaviour or ASD severity<sup>179,183</sup>.

Many of these early intervention approaches are based on models of typical development. Increasingly, studies are using a combination of methods to define treatment outcomes and to better understand the mechanisms and models of change of interventions. These methods include analysis of the degree to which changes in the direct target of the intervention (for example, parent behaviour) mediate later changes in child behaviour<sup>181</sup>, and the use of experimental methods such as EEG to examine whether there are accompanying changes in relevant brain networks<sup>184</sup>. Many parents seek complementary medical approaches, which to date have not been supported and sometimes are dangerous<sup>185</sup>. A note of general caution is that even in the context of significant treatment differences between groups, individual outcomes are very variable, and some children do not improve, although reliable predictors of response to treatment have not been demonstrated in rigorous, randomized controlled trials. As ASD is a heterogeneous developmental condition, different interventions may be required at different stages throughout life and different individuals might benefit from different interventions [Au: edits for brevity ok? Yes]. One area which many consider to hold much promise, that of neurobiologically or biomarker 'informed' psychological intervention, is on the horizon but such targeted therapies have not yet been developed.

## [H2] School age children and adolescents

Many children and young people with ASD can also benefit from interventions at later ages. A number of programs and approaches are available that focus on the core social communication difficulties of ASD; for example, social skills training programs for which moderate evidence of benefit exists<sup>186,187</sup>. In addition, non-verbal young people with ASD can benefit from use of augmentative communication systems, such as the Picture Exchange Communication System (PECS) that use picture symbols and behavioural training methods to allow children to request and make choices<sup>188</sup> or other technology-based augmentative communication systems. Increasingly, more generic interventions that target co-occurring emotional and behavioural problems are being adapted for youths with ASD, and initial studies suggest moderate benefits<sup>189</sup>. These interventions include modified cognitive behavioural therapy (CBT) for anxiety (modified, for example, to include parents, increase the duration of sessions, use more visual materials and specific work on understanding one's own emotion states)<sup>190</sup> and parent-mediated interventions for disruptive behaviour and ADHD<sup>191</sup>. More recently, there have been efforts to develop and test interventions that target aspects of parental wellbeing, such as parental stress and self-efficacy<sup>192</sup>. Increasingly, interventions for school-age children and young people with ASD are being delivered within the school environment, rather than the clinic, which has natural advantages for programmes that consist of groups or peer-to-peer interactions and an emphasis on social skills. Indeed, it is hoped that this approach may facilitate generalization of the skills learned<sup>193,194</sup>.

## [H2] Adult services

As individuals with ASD progress into and through adulthood, the focus of management shifts from treating the core symptoms of ASD to addressing associated symptoms or behaviours and promoting independence. However, there are few intervention studies to guide treatment options in adulthood. Indeed, a 2012 systematic review identified only 32 studies published between 1980 and 2010 that evaluated treatment studies for adolescents and young adults with ASD<sup>195</sup>. A more recent review identified 41 studies of interventions targeting social functioning in adults over a 37-year period<sup>196</sup>.

Despite the low number of treatment studies, there is some evidence supporting treatment efficacy for a limited number of symptoms, behaviors, and functional outcomes such as employment, social skills, and anxiety; however, in general, the evidence-base is weak<sup>195,196</sup>. For example, only three randomized controlled trials (all of which included small cohort sizes) that tested job interviewing skills curricula have been published. Social skills interventions have a somewhat more robust literature base (see <sup>196</sup> for review), but most of these studies had very small sample sizes and were not well controlled. In addition, it is unclear whether social skills interventions can be generalized to other social settings and situations, that is, whether skills learned in the treatment context are used by the participants in other settings, such as with peers or at work. There is some evidence for the use of cognitive-behavioural therapy (CBT) for effectively treating anxiety in people with ASD who do not have cognitive delays or language problems [Au:OK to add in this highlighted text? This was mentioned in the now-deleted 'Treatments for anxiety' section]<sup>197</sup>. However, nearly all of the existing research has been conducted with children and adolescents rather than in adults<sup>196</sup>, and individuals with substantial communication challenges are excluded from CBT studies. Furthermore, in contrast to the general population, CBT has not yet been shown to be effective for the treatment of depression in individuals with ASD. Given this weak evidence base, it may be fruitful to explore therapies and treatments tested in other groups that may benefit those with ASD.

Formal service systems and social care can help fill in the treatment gaps. Indeed, although many adults with ASD do not receive adequate services and support<sup>198</sup>, their receipt can improve outcomes across a number of domains<sup>158</sup>. For example, transportation services can allow adults with ASD to engage in employment and access therapies and programs in the community. In addition, comprehensive job support services can promote finding and maintaining employment, particularly for adults with more severe impairments<sup>199</sup>. Public health insurance can increase access to psychiatric care for those with co-occurring mental health problems, and income supports can reduce dependence on families.

## [H2] Medications

All medications that have evidence of benefit for ASD treat the associated symptoms or co-occurring diagnoses, rather than the symptoms of ASD directly (including social communication or repetitive behaviours). As mentioned earlier, ASD is an extremely heterogeneous disorder, and individuals with ASD can have a number of common co-occurring disorders that can also vary in severity.

Risperidone and aripiprazole (both of which are atypical antipsychotics) are approved in the USA to treat irritability and agitation — including aggression, self-injury and tantrums — in children and adolescents with ASD<sup>200–202</sup>. However, both treatments are associated with adverse events, including sedation, risk of movement disorders and weight gain, which limit their use to people with severe irritability with agitation<sup>202</sup>. The anti-diabetes drug metformin has been shown to limit weight gain from these medications, possibly broadening their safe use<sup>203</sup>.

As mentioned previously (see Co-occurring disorders, above), co-occurring mental health conditions are common in people with ASD. Methylphenidate, atomoxetine and guanfacine are beneficial for ADHD symptoms in ASD (Table 2<sup>204–206</sup>) [Au: given that these medications target different symptoms of ADHD are they ever prescribed in combination? Or will a child be given one medication only?] . Although serotonin reuptake inhibitors (SRIs), such as fluoxetine and citalopram, are used for the treatment of depression, anxiety and OCD in the general population, they have differing efficacy in people with ASD [Au:OK?] . Indeed, although fluoxetine improves symptoms [Au: all symptoms?] of OCD in adults with ASD<sup>207</sup>, citalopram has demonstrated poor tolerability and no benefit for repetitive behaviour in children with ASD<sup>208</sup>. Medications for depression or anxiety have not systematically been tested in people with ASD.

[Au: as this text is very future-looking, would it be best placed in the Outlook section?] Some excitement has accompanied the recent studies of medications targeting the neurohormonal oxytocin or vasopressin systems, both of which modulates social behaviour across species. Underpowered studies of intranasal oxytocin have demonstrated mixed results that are overall not supportive of a large effect size<sup>209,210</sup>, with results pending from adequately powered studies [Au: please provide the NCT number of this ongoing study here so readers can follow up in due course] . In addition, a pilot study of intranasal vasopressin suggested possible benefit in people with ASD, although this study was underpowered<sup>211</sup>. A large trial of balovaptan, a vasopressin AVPR1A antagonist in adults with ASD showed negative results on its primary outcome ( a general rating of ASD symptoms), with suggestive results on a key secondary parent report measure of adaptive behaviour, including social and communication behaviour<sup>212</sup>. A few studies have also focused on the hypothesis that, at the level of neural circuits, ASD may result from excessive excitation or insufficient inhibition<sup>213</sup>, with some promising but inconclusive results for medicines that target the GABAergic system<sup>214</sup>. Medications targeting genetic syndromes that can cause [Au:OK?] ASD have not yet yielded consistent improvement<sup>215,216</sup>, but there is much hope for a precision medicine approach that links genetic subgroups with neurobiology-based treatments.

## [H1] Quality of life

### [H2] Objective and subjective measures

Several aspects of intervention research speak straight to the heart of current debates within the clinical field and broader ASD community, including how a good outcome is classified for an individual with ASD, as well as who should decide what outcomes are used [Au: edits for style ok?] in intervention studies<sup>217</sup>. This point is aligned both with the debates about medical versus social models of disability but also with a more general shift in medicine away from focusing on symptom reduction to improving the wellbeing and quality of life (QOL) of patients. QOL research in adults with ASD has focused on two aspects: objective and subjective QOL. Objective QOL encompasses social achievements such as employment, adequate living conditions, supportive relationships, and good physical and mental health<sup>218</sup>, whereas subjective QOL focuses on individuals' perceptions and subjective assessments of their own lives<sup>219</sup>. Both subjective and objective QOL are often related, but not synonymous, and both are important to take into account when considering outcomes for individuals with ASD (Table 3).

**[H3] Objective QOL.** Adults with ASD tend to have poor objective QOL. Unemployment is high in this population, and even among those employed, individuals are often working below their skills and abilities<sup>220,221</sup>. Moreover, independent living can be **[Au:OK? As presumably some individuals may be able to live independently with relative ease?]** a challenge, and adults often lack meaningful relationships with peers<sup>222</sup>. When aggregating across these domains of life, many adults with ASD have ‘poor’ or ‘very poor’ outcomes<sup>223,224</sup>.

ASD is a highly heterogeneous condition and several factors have been associated with higher versus lower objective QOL. Most of the studied factors associated with higher objective QOL have been characteristics of the individuals (versus families, service system or communities), and consistent predictors of higher objective QOL include better early language development **[Au:OK?]**, higher IQ and adaptive behaviour scores, less severe ASD symptoms, and fewer challenging behaviours<sup>225</sup>. In addition, more recent research suggests that women with ASD may have a more difficult time maintaining employment positions<sup>226</sup>, and are more likely to ‘camouflage’ their ASD symptoms than men, which can lead to mental health challenges<sup>227</sup>.

**[H3] Subjective QOL.** Meta-analysis have suggested that across the lifespan, subjective QOL tends to be lower among individuals with ASD compared to typically-developing peers<sup>228</sup>, but is often more positive than indicators of objective QOL<sup>223,229</sup>. Predictors of subjective QOL tend to be inconsistent across studies, except for perceived stress and supports, the latter of which encompasses services, family and social support<sup>230–232</sup>.

## **[H2] Self-advocate perspective**

**[Peer reviewer comment: The self-advocate perspective is important. It was quite noticeable to use identity-first language (“autistic people”) only in this section and some explicit reference to this choice might be made, to help readers understand the politics and differing viewpoints.]** It is clear that ASD has heterogeneous outcomes and biological underpinnings; what is less clear-cut are the differing and nuanced views of autistic people regarding how ASD should be approached and researched (**Box 2**, Autistica<sup>233</sup>, see also Ontario Brain Institute<sup>234</sup>). Indeed, some people with a diagnosis see ASD as being a fundamental part of their identity whereas other people do not. In addition, many people feel that social change is required<sup>235</sup>, whereas other individuals want therapies to meet a range of their needs<sup>236</sup>. The key is respect for a variety of views and ultimately respect for autistic people. Researchers can demonstrate respect by considering how ASD as a topic is distinct from, for example, cancer. To this end, terms like ‘disease’ are inappropriate and are scientifically inaccurate when referring to ASD. Ultimately, active participation in the design, implementation and interpretation of research studies **[Au:OK?]**, clear consideration of research ethics and the consequences of research involvement, and broad consultation of autistic people in research is key to authentically addressing the substantial inequalities autistic people face as a group and ensuring they live long, healthy, happy lives.

## **[H2] Family perspectives**

Families of people with ASD are also heterogeneous, yet, as a group, they experience lower QOL than families with a member with other neurodevelopmental conditions, even before receiving the formal diagnosis<sup>237</sup>. For this reason, it is essential that parents, other family members, clinicians, educators, and

the entire external support system coalesce around common goals for outcomes whilst accessing and maximizing resources for the betterment of the child and family. Parents are typically at the centre of this support network and carry much of the responsibility of direct care, coordination and advocacy, over and above typical parental responsibilities<sup>238,239</sup>. The exact parental roles are dependent on the child's strengths and challenges, and frequently shift over time (Fig. 6). During this process, it is important that parents maintain motivation by setting realistic goals and tracking progress to experience the many achievements that their loved one with ASD can attain.

Effective parents often work closely with experienced providers who can track development of the child with ASD and can provide guidance on next actions<sup>240</sup>. Early in childhood [Au:OK?] , this role includes identifying and engaging with early and school-based interventions. It is never too early for parents to begin planning for the adult transition process, including (dependent on the person with ASD's capacity) promoting self-advocacy, preparation for life after secondary education, vocational training and employment supports, living needs, community participation, and long-term financial considerations. During adulthood, for cognitively-able adults, parental roles might shift to more traditional relationships<sup>241</sup>, whereas for those with cognitive disability, parental caregiving often continues and culminates in planning for late life needs<sup>242</sup>. Although the journey can be challenging, for many parents, it can be incredibly rewarding and a source of life meaning.

Many parents recognize the need to give back to the community [Au:OK?] through research. Accordingly, it is crucial that researchers foster this desire carefully, communicating with parents to ensure that any potential immediate or future risks or benefits are clear. Even if the study period is brief, in many cases, the goal should be to develop a positive longer-term relationship, as this can lead to parents and people with ASD continually re-engaging in and developing positive feelings about the research process.

## [H1] Outlook

ASD research has substantially expanded in the past 50 years, particularly the past 20 years, as reflected in the websites listed in Box 3. Although it seems unlikely that the incidence of ASD is truly rising at the rate suggested in prevalence studies, these data have increased awareness and the numbers of diagnosed children in schools and clinics, although adult services and recognition run far behind. The lives of people with ASD diagnoses have improved at least in some high-income countries, with a greater proportion of children using some language<sup>243</sup>, more adults with educational qualifications and less institutionalization<sup>243</sup>, although the changing nature of diagnoses has to be considered when interpreting historical trends. Some risk factors for ASD have been identified (such as increased parental age, birth trauma and a positive family history) which has implications at least for more careful follow-up. In addition, the genetics of ASD has yielded surprising discoveries with substantial implications for heritable neurodevelopmental disorders, such as ADHD, language delay and named syndromes associated with profound intellectual disability. The perceived value of routine genetic screening for ASD diagnosis is disputed, [Au: edits ok?] , with American medical academies strongly in favor whereas those in other countries much more selective. Studies of brain structure and function have added similarly intriguing findings that are just beginning to be integrated into both developmental and more mechanistic models of behaviour with possible targets or markers for change. Despite the intellectual contribution of these studies to research, at this point, neither EEG nor imaging are recommended as part of standard practice for diagnosis of [Au:OK?] ASD but can be used for other neurological indicators (such as if there are concerns beyond ASD symptoms that merit an EEG or imaging). In this field, replication of findings across



sites and even within individuals, as well as larger samples through collaboration are the promise of the future.

One way of bringing the three themes of mechanisms, heterogeneity and outcomes of ASD together is to consider the trajectories of this disorder over time (Fig. 7), and how knowledge of these trajectories can contribute to investigations of the biological and cognitive underpinnings of ASD, and how treatments and supports could make the lives of children and adults with ASD more positive.

In terms of mechanisms, despite earlier hopes for simple genetic explanations of ASD, instead, we have identified many single gene germline loss of function point mutations yielding some initial models of disruption in very basic molecular patterns, as well common genes with small effects that are just beginning to emerge<sup>29</sup>. Attempts to study genes-first have shown heterogeneity even within highly specific CNVs, with a few exceptions. In addition, hope exists that genetically based interventions for ASD may be possible, although this will likely involve much further research . **[Au: please advise how to proceed here - would you like to move this text back?]** Indeed, given the success and approval of gene therapy for early onset neurological disorders, particularly spinal muscular atrophy (SMA) type 1<sup>244,245</sup>, targeting single genes of large effect in both idiopathic and monogenic ASD is being viewed as increasingly plausible. As rare syndromes such as fragile X syndrome, angelman syndrome and rett syndrome have offered some of the earliest insights into ASD biology, these disorders are also likely to lead the way in illuminating the practical and important ethical challenges that will attend such efforts for idiopathic ASD. Efforts aimed at the highest confidence risk genes identified in idiopathic ASD, such as *SCN2A* and *CHD8*<sup>34,35</sup>, are almost certain to soon follow on attempts at gene therapy for monogenic neurodevelopmental disorders, in light of the growing list of well-defined large-effect targets, the increasing options for addressing haploinsufficiency<sup>246</sup>, the ability to manipulate gene products without leaving a DNA “scar”<sup>246,247</sup> and the increasing ability to readily detect mutations—and intervene—in utero and very early in post-natal development.

Data from genetic approaches that might yield targeted genetic interventions may be most relevant to rare, severe neurodevelopmental difficulties in general rather than ASD as a specific entity. With more information about the differing developmental trajectories of ASD, more continuous measures of symptoms and measures of language and intellectual function, behavioural phenotypes and changes over time can be quantified across different neurobiologically defined subgroups. This approach could potentially identify different ‘routes’ to different outcomes, whether ASD or not, and could have a practical benefit in terms of selecting and monitoring appropriate treatments. In addition, with the heterogeneity of ASD, our growing understanding of mechanisms, be they causal or mechanisms for change, needs to be linked to trajectories in development and not be considered as static<sup>248</sup>. Researchers modelling ASD in other species might find the incorporation of early developmental manifestations, such as regressions or motor delays, more tractable than the current focus on ASD- related social communication symptoms seen in humans. With collaborations and studies of sufficient sample sizes, investigators have begun to focus on findings within different developmental periods that could provide insight into trajectories and targets for intervention. Thus, more study of the development of ASD both in studies of human behaviours and in animal models might have an effect on the identification and treatment of ASD as a neurodevelopmental disorder. Prospective studies, including epidemiological and direct behavioural work across developmental periods, moving beyond very young children to later childhood, adolescence, and adulthood are needed.



Similarly, limited findings about adult development and patterns that lead into ASD (Figs 5 and 7), call for measurement of different outcomes that respect individual differences in autistic people and in families (Box 2). By young adulthood, available supports for places to live, employment and mental health services are needed for individuals who have a range of skill levels, with supports not always well matched to the needs of individuals; however, comparisons of treatments or treatment intensities have not historically been made, even though they are continually called for. The types and specific goals of treatments differ greatly for autistic people who are verbally fluent versus those who have difficulty speaking for themselves, such that alternative systems need to be in place that take into account co-occurring conditions, strengths, preferences and challenges. More studies of well-defined, more homogeneous subgroups of autistic children and adults over time would provide different and more useful information about real-life issues, as in Table 3 than large-scale surveys of very heterogeneous samples<sup>249</sup>.

Progress in the biology of more generally defined neurodevelopmental disorders may have the greatest yield for children with ASD in their early years [Au: compared with what? In their later years?]. Clinical trials that compare known treatments (both psychosocial and biological), with new ones and treatment as usual would allow us to build on previous findings in a more meaningful way and begin to address the priorities listed in Box 2, which strikingly, are seldom priorities in autism research. To move from science to practice including evaluation and treatment, ASD researchers need to find a way to select and fund studies of more mundane, but critical evidence gaps in understanding heterogeneity, mechanisms of change and outcome that affect practice in any circumstance, not just internationally, within academic systems that reward creativity and novelty. Unique methodologies, including the baby sibling studies, accumulation of large data sets (such as ABIDE, and the Simons Simplex Collection (SSC)), prospective epidemiological studies and mechanistic studies of intermediate biomarkers may begin to bring together information from molecular to pathophysiological to cognitive and behavioural levels. However, for now, as for other neurodevelopmental and psychiatric disorders including schizophrenia<sup>250</sup>, the distance between science and practice remains great, and the amount of research that attempts to address solvable problems for autistic people alive today and their families remains modest.

## Box 1. Global challenges in autism research

Recently, there have been calls for more attention to global issues in autism research<sup>249</sup> (Global Research on Developmental Disabilities Collaboration – Lancet Global Health, 2016), including a number of related issues with somewhat different potential solutions. For example [Au: edits to improve the narrative flow ok?] , broader populations should be included in autism research, including individuals from Lower Resource and Middle Income countries (LMICs), but also inclusive representation of the ethnic, linguistic and socio-economic diversity of many High Resource countries and people whose autism is unrecognised. Moreover, there should be the creation of opportunities to carry out research in LMICs <sup>251</sup>(Patel et al, 2015). Open source and shared databanks, including autism-specific resources such as the Simons Simplex Collection and Autism Brain Imaging Data Exchange [Au:OK?] (ABIDE), as well as broader collaborations such as PsychENCODE [Au:OK?] could assist in promoting international research [Au: edits for brevity ok?] . In addition, the science of autism should be disseminated in ways that are useful for practice in all countries, [Au: edits ok?] but with particular attention to the needs of communities and families with fewer resources <sup>252 253</sup>. [Au: sentence deleted as suggested] More immediately, searches for scalable methods of identification and perhaps intervention with children and adults [Au:OK? Yes] with autism<sup>135,254</sup> have begun [Au: globally or in LMICs?] . However, the need to develop scalable global practices highlights how little is known about when we need **population-wide testing** for autism versus broader neurodevelopmental disorders, the minimal intensity and duration of effective interventions, behavioural mechanisms behind changes in behaviour and which treatments work with which children and adults and families, all of which have a bearing on interventions locally and globally. In addition, global issues of stigma, governance and paucity of resources also have to be taken into account <sup>251</sup>.

**Box 2. Top ten questions for ASD research proposed by autistic people, family members and professionals. (Reference: Autistica<sup>233</sup>)**

1. Which interventions improve mental health or reduce mental health problems in people with autism spectrum disorder (ASD)? How should mental health interventions be adapted for the needs of people with ASD?
2. Which interventions are effective in the development of communication and language skills in ASD?
3. What are the most effective ways to support or [Au:OK? Our style is to avoid solidus as the meaning can be ambiguous] provide social care for autistic adults?
4. Which interventions reduce anxiety in autistic people?
5. Which environment supports are most appropriate in terms of achieving the best education, life and [Au:OK?] social skills outcomes in autistic people?
6. How can parents and family members be supported and/or educated to care for and better understand an autistic relative?
7. How can ASD diagnostic criteria be made more relevant for the adult population? And how do we ensure that autistic adults are appropriately diagnosed?
8. How can we encourage employers to apply person centred interventions and support to help autistic people maximize their potential and performance in the workplace?
9. How can sensory processing in ASD be better understood?
10. How should service delivery for autistic people be improved and adapted in order to meet their needs?

**Box 3. Examples of ASD websites** [Au: based on Tony's comment I've introduced some broader headings here rather than adding a description under each individual website - what do you think? Please check carefully and let me know if you prefer the original version (we can revert the changes, no problem!)]

**Sites for health care professionals or research scientists:**

**[H1] American Academy of Pediatrics**

<https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Pages/autism-initiatives.aspx>

**[H1] International Society for Autism Research**

**ASD:**

<https://www.autism-insar.org>

**[H1] National Autistic Society**

<https://www.autism.org.uk>

**[H1] Royal College of General Practitioners**

<https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/asd-toolkit.aspx>

**Information about treatment, research and advocacy for people with ASD and their families:**

**[H1] Autism Canada**

<https://autismcanada.org>

**[H1] Research Autism**

<http://www.researchautism.net/>

**[H1] Autism Europe**

<https://www.autismeurope.org/>

**[H1] Autism India**

<http://www.autism-india.org>

**[H1] WHO**

<https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders>

**[H1] Autism Spain**

<http://www.autismo.org.es>

**[H1] Autism Speaks**

[www.autismspeaks.org](http://www.autismspeaks.org)

**[H1] Autismus Deutschland**

<https://www.autismus.de>

**[H1] Autistica**

<https://www.autistica.org.uk>

**Information about research funding, and up-to-date information for people with ASD and families:**

**[H1] Simons Foundation**

<https://www.sfari.org>

**[H1] US NIH**

<https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd/index.shtml>

**[H1] Autism Science Foundation**

<https://autismsciencefoundation.org>

**Epidemiological information [Au:OK?]**

**[H1] US CDC**

<https://www.cdc.gov/ncbddd/autism/index.html>

**Figure 1.** Theories and findings regarding ASD mechanisms, outcomes and heterogeneity.

Original descriptions of the cardinal features of autism spectrum disorder (ASD) were attributed to a range of causes including being raised by wolves (the Wild Boy of Aveyron), inborn limitations in affective contact and unfeeling parenting (such as ‘refrigerator mothers’) and holy people (such as fools for Christ))<sup>255</sup>. Conceptualizations of ASD as a common highly heritable neurodevelopmental disorder with underlying cognitive features began with the recognition of differences in brain function and cognition in the 1960s<sup>256–259</sup> and the first twin study in the 1970s<sup>260</sup>. Other proposed mechanisms include maturational lags in neurophysiology<sup>90</sup> and cognitive mechanisms such as joint engagement<sup>171,261</sup>. With the search for pathways to and sometimes out of ASD<sup>262</sup> on many levels, conceptualization of positive outcomes has been more recent, but has also varied markedly. In the 1970s, autism societies and collaborative clinical programs focused on community integration and de-institutionalization (such as National Autistic Society (NAS) and National Society for Autistic Children (NSAC))<sup>263</sup>. Priorities shifted in the 1980s and 1990s, with still unreplicated claims of ‘recovery’ in children who participated in intensive behavioural interventions<sup>174</sup>, new advocacy groups focusing on biomedical discoveries to yield potential biological treatments and even ‘cures’ (such as National Alliance for Autism Research (NAAR) and Cure Autism Now<sup>255</sup>) and the neurodiversity movement<sup>264</sup> which rejected ‘cures’ and called for adaptation of environments to support autistic people, using terminology preferred by self-advocates and community participation. Recognition of the marked heterogeneity within ASD began in the 1970’s with the triad of impairments in language, play and social interaction characterizing many children with intellectual disabilities (ID) or those with classical autism<sup>265</sup>. The first twin study demonstrated that monozygotic twin pairs, though concordant for difficulties associated with ASD, differed in specific characteristics and co-occurring conditions including ID<sup>260</sup>. More recently, phenotypic heterogeneity has been the rule in most, though not all, gene-first phenotypic studies<sup>266</sup>. Thus, developmental aspects of differences in strengths, difficulties and trajectories, as well as biological factors, require highly personalized conceptualizations of the needs of autistic individuals and their families. ABA, applied behaviour analysis; AGRE, Autism Genetic Resource Exchange; CDC, US Centers for Disease Control and Prevention; DSM, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalography; GRASP, Global and Regional Asperger

Syndrome Partnership ;IDEA, Individuals with Disabilities Education Act; MCEP, the gene associated with Rett Syndrome; PACT, Preschool Autism Communication Trial; PDD, pervasive developmental disorder; SNAP, Special Needs and Autism Project; SPARK, Simons Foundation Powering Autism Research for Knowledge, TEACCH, Treatment and Education of Autistic and Communication related handicapped Children.

**Figure 2.** Environmental risk factors for ASD.

Data from studies aiming to identify risk factors for autism spectrum disorder (ASD) can be broadly split into three categories, those with evidence supporting an association (panel a), those with inconclusive evidence (panel b) and importantly, those with no supporting evidence (panel c). Bars represent ranges. \*Represents recurrence risk. Figure adapted from <sup>18</sup> with added findings from select reviews and empirical papers: neonatal hypoxia estimate<sup>267</sup>, childhood vaccines<sup>20</sup>, valporate use during pregnancy<sup>268</sup>, parent age estimates<sup>269</sup>, preterm birth estimate<sup>270,271</sup>, maternal obesity estimate<sup>272</sup>, folic acid intake estimate<sup>273</sup>, siblings estimate<sup>274,275</sup>, interpregnancy interval estimate<sup>276</sup>, assisted reproductive technologies estimate<sup>277,278</sup>, pesticide and air pollution estimate<sup>279</sup>, caesarian section estimate<sup>280</sup>.

**Figure 3.** Encoded proteins associated with ASD risk. [Au: please ensure this figure is added to the third party rights table and we will obtain permission to reuse it on your behalf. Note that I've added the protein names in after the ASD syndromic genes, below ]

Simplified schematic of the major cellular components of a neural circuit in the cerebral cortex, with a focus on pyramid-shaped glutamatergic excitatory projection neurons. Proteins encoded by selected high-confidence (FDR < 0.1) autism spectrum disorder (ASD) risk genes<sup>34</sup> and proteins encoded by selected syndromic ASD genes have a role in these neurons during development. These proteins have a diverse intracellular distribution; those at the synapse, have roles in cell adhesion, scaffolding and signalling. In addition, some of these proteins are localized to the nucleus and have been shown, broadly, to mediate chromatin modification and transcriptional control. Syndromic ASD genes include *FMR1* (encoding fragile X mental retardation protein; fragile X syndrome), *UBE3A* (encoding Ubiquitin-protein ligase E3A; Angelman syndrome), *TSC1* and *TSC2* (encoding hamartin and tuberlin; tuberous sclerosis complex), *PTEN* (encoding Phosphatase and tensin homolog) and *MECP2* (encoding methyl-CpG-binding protein 2; Rett syndrome). Adapted from <sup>48</sup>.

**Figure 4.** Longitudinal trajectories of total brain volume, surface area and cortical thickness in ASD.

[Au: please ensure this figure is added to the third party rights table and we will obtain permission to reuse it on your behalf] Brain trajectories from 6–24 months of age for total brain volume (TBV, panel a), surface area (SA, panel b) and cortical thickness (CT, panel c). [Au: These data are quite complex and may be difficult for non-experts to understand; accordingly, please briefly describe the key trends in this figure in 2-3 sentences, what are the take-home messages from the figure?] Corrected age [Au: edited Length-age to 'corrected age' as per the original figure, ok?] refers to the age corrected by length (body size).. From Hazlett et al. 2017.

**Figure 5.** Co-occurring disorders [Au: this title was too long to adhere to our production guidelines so I've edited it down, ok? I've tried to incorporate the original title into the first line of the legend, is this ok?] .

Primary and secondary disorders and disadvantage can accumulate through development in people with autism spectrum disorder (ASD). These disorders can form additional targets for treatment and policy. Prevalence [Au:OK?] estimates from QUEST<sup>281</sup> SNAP<sup>133,282</sup> and EDX<sup>142</sup> cohorts [Au: please advise on how to proceed with Terry's comment here] .

**Figure 6.** Major parental milestones in advocating and supporting their child with ASD.

Families of children and adults with autism spectrum disorder (ASD) have many decisions and expectations across the lifespan of their children, from seeking initial diagnostic evaluation and intervention to preparing for aging-related services. These decisions [Au:OK?] vary across different cultures, regions and countries and depend on many factors, including the resources and services available. However, several decisions are common across all regions [Au:OK?] , including LMR [Au: please define LMR - do you mean LMICs?], such as choices about who will care for their child if the parents are temporarily unable [Au: edits for brevity ok?] , the amount of time parents and other family members can spend with the child with ASD versus meeting other needs, ways to modify their home environment to ensure the safety and independence of the individual with ASD and the kinds of behavioural expectations that are most helpful for their child or adult. Of note, for many families, these choices and responsibilities are lifelong and are relevant, for children, adolescents [Au:OK?] , adults and elders [Au:OK?] with ASD.

**Figure 7.** Changes in daily living scores as predicted by IQ scores and autistic symptoms.

Changes in independent daily living skills can be observed in people with ASD over time. This sample consists of ~100 young adults with a mean age of 26 years with autism spectrum disorder (ASD), who were evaluated at 2, 3 and 9 years of age and followed up to 26 years of age. [Au: I've incorporated the discussion of how these scores were obtained and what they mean below (highlighted in yellow) for flow, ok? Text discussing divergence and heterogeneity moved to later on in the legend for flow] Daily living scores [Au: instead of 'outcomes', ok?] are very diverse, ranging from age-appropriate levels of independence at adulthood (represented by a daily living score of 100 , assessed using the Vineland II<sup>283</sup> [Au:OK?] ) to very limited skills (represented by a score of <30). [Au: green text moved to here from earlier on for flow] Increasing divergence shows where measurement after 2 years of age is additionally predictive, with the line thickness indicating the proportion of early referred children that followed each trajectory. Heterogeneity in intellectual functioning and severity of ASD symptoms (social communication and restricted, repetitive, sensory behaviors) can be observed. In addition, improvements and worsening of autistic symptoms and intellectual functioning can occur over time. A, B| Referred children had verbal IQs predominantly <50 (over 3 standard deviations below average) but could show improvement in daily living standard scores [Au:OK?] from 2 to 3 years of age that were indicative of eventual greater independence in adulthood. Relatively less early change in non-verbal IQ is seen but, like verbal IQ, by



1108 adulthood the association with eventual adult daily living skills is strong. C, D | Variation in ASD symptom  
1109 severity in social-communication (CSS refers to The Autism Diagnostic Observation Schedule, Second  
1110 Edition (ADOS-2) Comparison Scores) showed a stronger association with adult independence than  
1111 restricted-repetitive behaviours and continued to change over the lifespan following more divergent  
1112 pathways than intellectual functioning. Data from the EDX cohort compiled from <sup>1,142,284</sup>.

1113

**Table 1:** ASD as defined in DSM-5.

[Au: I do think this version is improved, however, we can no longer include bullet points within tables as this leads to problems at the layout stage - what about converting this to a text box (see example below)]

Domains		Other criteria
A. Social communication and social interaction	B. Restricted, repetitive behaviours and interests	
Must have evidence across multiple contexts of all 3 subdomains currently or by history	Must have evidence of 2 of 4 subdomains currently or by history	C. Symptoms must be present in early development but may not be fully manifest until later or may be masked later in life by learned strategies
Subdomains	Subdomains	D. Symptoms must cause clinically significant impairment in current functioning
<ul style="list-style-type: none"> <li>Social reciprocity</li> <li>Nonverbal communication</li> </ul> <p>Developing, maintaining and understanding relationships</p>	<ul style="list-style-type: none"> <li>Stereotyped, repetitive behaviours</li> <li>Insistence on sameness</li> <li>Highly restricted, fixed interests</li> </ul> <p>Hyper- or hyposensitivity or interest in sensory inputs</p>	
<b>Note:</b> Previously established DSM-IV diagnoses of any pervasive developmental disorder, including Asperger's disorder should be assumed to be equivalent to DSM-5 ASD	<b>Note:</b> ASD may co-occur with many other disorders including ADHD, intellectual disability, language delay and genetic syndromes	E. Not better explained by intellectual disability or global developmental delay

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DSM-5, Diagnostic and Statistical Manual of Mental disorders, Fifth Edition.

#### **Box xx. ASD as defined in DSM-5.**

The Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5) criteria for autism spectrum disorder (ASD) comprise 5 symptom clusters (A-E)

A. Social communication and social interaction.

- Must have evidence across multiple contexts of all of the following 3 subdomains currently or by history
  - Social reciprocity
  - Nonverbal communication

1131                   ○ Developing, maintaining and understanding relationships

1132

1133   B. Restricted, repetitive behaviours and interests.

1134           • Must have evidence of 2 of 4 of the following subdomains currently or by history

1135                   ○ Stereotyped, repetitive behaviours

1136                   ○ Insistence on sameness

1137                   ○ Highly restricted, fixed interests

1138                   ○ Hyper- or hyposensitivity or interest in sensory inputs

1139

1140   C. Symptoms must be present in early development but may not be fully manifest until later or may be  
1141   masked later in life by learned strategies

1142

1143   D. Symptoms must cause clinically significant impairment in current functioning

1144

1145   E. Not better explained by intellectual disability or global developmental delay

1146

1147   Note: Previously established DSM-IV diagnoses of any pervasive developmental disorder, including  
1148   Asperger's disorder should be assumed to be equivalent to DSM-5 ASD. ASD may co-occur with many  
1149   other disorders including ADHD, intellectual disability, language delay and genetic syndromes.

1150

1151 **Table 2:** Evidence-based medication in ASD (adapted from Lord et al<sup>285</sup>) [Au: please ensure this is added  
1152 to the third party rights table and we will obtain permission to reuse it on your behalf]

<i>Medication</i>	<b>FDA or EMA Indication and age</b>	<b>Effect Size (d)</b>	<b>Common Adverse Effects</b>
<b><i>Typically used for ADHD symptoms</i></b>			
<i>Methylphenidate</i>	FDA and EMA approval for ADHD (not specific for ASD) in those ≥ 6 years of age [Au: edits ok?]	d=0.78 (teacher rated)	Sleep disruption and decreased appetite
<i>Atomoxetine</i>	FDA and individual country approval for ADHD (not specific for ASD) in those ≥ 6 years of age [Au: edits ok?]	d=-0.68--0.84	Decreased appetite, nausea and irritability
<i>Guanfacine</i>	FDA and EMA approval for ADHD (not specific for ASD) in those 6–17 years of age [Au: edits ok?]	d=1.67	Fatigue, sedation and decreased pulse and blood pressure [Au:OK?]
<b><i>Typically used to treat agitation and irritability</i></b>			
<i>Risperidone</i>	FDA approval for irritability associated with ASD and EMA approval only for other indications [Au: what indications?] in those 5–17 years of age [Au: edits ok?]	d=0.94	Increased appetite, sedation and weight gain
<i>Aripiprazole</i>	FDA approval for irritability associated with ASD and EMA	d=0.87	Nausea and weight gain

	approval only for other indications [Au: what indications?] in those 6–17 years of age		
--	--	--	--

1153 ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; EMA, European  
1154 Medicines Agency.  
1155

1156 **Table 3:** Factors that affect QOL. Cited within table: (Duncan & Bishop<sup>286</sup>) **[Au: please ensure this is**  
 1157 **added to the third party rights table and we will obtain permission to reuse it on your behalf]**

Type of QOL	Factor	Description
Objective QOL	Early language	Follow-up studies of adults with ASD who were diagnosed as children have examined the amount of spoken language during early childhood. Individuals with ASD who had fluent speech are more likely to have higher levels of objective QOL life in adulthood than those with phrased speech or those with no speech or who spoke in single words.
	Indicators of intelligence	Studies examining IQ scores using standardized IQ tests administered both in early childhood and adulthood find that individuals with ASD and higher IQ scores have higher levels of objective QOL than those with lower IQ scores <b>[Au: comparator ok?]</b> . Other, less-standardized measures of intelligence (such as those used in large cohort studies <b>[Au: what measures? Please provide another example here]</b> ) have similar findings.
	Adaptive behaviour	Higher levels of adaptive behaviour – and particularly more activities of daily living – are associated with better objective QOL in people with ASD. Adaptive behaviour is a challenge for many individuals with ASD, who have scores below what would be expected based on IQ <sup>286</sup> . Adaptive behaviour is changeable, making it a promising avenue for interventions to improve objective QOL.
	Autism symptom severity	Individuals with more severe autism symptoms tend to have lower objective QOL in adulthood.
	Challenging behaviours	Higher levels of challenging behaviours in people with ASD, which can include both internalizing problems and externalizing problems, are related to lower objective QOL.
	Sex or gender	Sex or gender associations with objective QOL have been demonstrated in terms of employment or post-secondary education. Indeed, women with ASD obtain employment and post-secondary educational positions at the same rate as men with ASD but have a more difficult time maintaining those positions over time.
Subjective QOL	Perceived stress	Many adults with ASD perceive high levels of stress in their own lives. These perceptions are related to lower subjective QOL.
	Supports	Several different types of supports have been related to subjective QOL, including formal services, support from family members (most often parents) and more general social support from others.

1158 ASD, autism spectrum disorder; QOL, quality of life.

## References

### Highlighted references:

1. Sadowsky J. John Donovan, Carrie Zucker. In a different key: The story of autism. *J Hist Behav Sci.* 2018 Jan;54(1):66–7.

**This paper presents a different, broad overview of the changes in perspective about autism and ASD over the years.**

2. Brugha TS, Spiers N, Bankart J, Cooper S-A, McManus S, Scott FJ, et al. Epidemiology of autism in adults across age groups and ability levels. *Br J Psychiatry.* 2016 Dec;209(6):498–503.

**This paper uses active case-finding to provide representative estimates of the prevalence of ASD and demonstrated that rates of ASD in men and women were equivalent in adults with moderate to profound intellectual disability.**

3. Hazlett HC, Gu H, Munsell BC, Kim SH, Styner M, Wolff JJ, et al. Early brain development in infants at high risk for autism spectrum disorder. *Nature.* 2017 Feb;542(7641):348–51.

**This seminal paper, through careful recruitment and methodology was the first to show significant early differences that may contribute to our understanding of developmental features in neural structure and circuits.**

4: Jamain, S., Quach, H., Betancur, C., Råstam, M., Colineaux, C., Gillberg, I. C., ... & Bourgeron, T. (2003). Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nature genetics*, 34(1), 27.

**This was the first paper to show a de novo loss of function mutation in a synaptic gene associated with non-syndromic ASD and really was a harbinger for so many of the findings that came after.**

5. Sebat, J., Lakshmi, B., Malhotra, D., Troge, J., Lese-Martin, C., Walsh, T., ... & Leotta, A. (2007). Strong association of de novo copy number mutations with autism. *Science*, 316(5823), 445-449.

**This paper was the first to focus explicitly on simplex autism and show the importance of de novo CNVs in simplex cases, versus familial cases, versus controls.**

6. Dumas G, Soussignan R, Hugueville L, Martinerie J, Nadel J. Revisiting mu suppression in autism spectrum disorder. *Brain Res.* 2014 Oct;1585:108–19.

**Paper replicating the mu suppression deficits in autism during action observation but questioning through high-density spectral analyses and sources reconstruction its previously drawn relation to the MNS.**



1191 7. Schilbach L. Towards a second-person neuropsychiatry. *Philos Trans R Soc B Biol Sci.* 2016 Jan  
1192 19;371(1686):20150081.

1193 **Review supporting that psychiatric disorders are more commonly characterized by impairments of**  
1194 **social interaction rather than social observation, and advocating for an interactive turn in**  
1195 **neuropsychiatry.**

1196

1197 8. Durkin MS, Elsabbagh M, Barbaro J, Gladstone M, Happe F, Hoekstra RA, et al. Autism screening and  
1198 diagnosis in low resource settings: Challenges and opportunities to enhance research and services  
1199 worldwide. *Autism Res.* 2015 Oct;8(5):473–6.

1200 **This is a position paper highlighting challenges to translating knowledge on better awareness,**  
1201 **understanding, identification, diagnosis (and then treatments) from the past two decades of clinical**  
1202 **research in HICs into LMICs**

1203 9. Lord C, Risi S, DiLavore PS, Shulman C, Thurm A, Pickles A. Autism From 2 to 9 Years of Age. *Arch Gen*  
1204 *Psychiatry.* 2006 Jun 1;63(6):694.

1205 **This paper clearly establishes that autism was a stable diagnosis (as a spectrum) beginning at least by**  
1206 **age 2. The paper also established parent interview and clinician observation as predictive of autism at**  
1207 **age 9. Finally, it was the first paper that showed that the specific DSM-IV-TR diagnoses were unstable**  
1208 **across childhood but that the instability was almost all shifting across categories not outside the**  
1209 **spectrum.**

1210 10. Ozonoff S, Iosif A-M. Changing conceptualizations of regression: What prospective studies reveal  
1211 about the onset of autism spectrum disorder. *Neurosci Biobehav Rev.* 2019 May;100:296–304.

1212 **Despite its potential importance as biological marker and/or subgroup of ASD, developmental**  
1213 **regression has remained very poorly understood. This paper outlines recent data and**  
1214 **reconceptualization about patterns of onset (and loss) that chimes with a more contemporaneous**  
1215 **understanding of ASD as a heterogeneous condition in terms of its manifestation both within and**  
1216 **across individuals.**

1217

1218 1. Lord, C. *et al.* Autism From 2 to 9 Years of Age. *Arch. Gen. Psychiatry* **63**, 694 (2006).

1219 2. Risi, S. *et al.* Combining Information From Multiple Sources in the Diagnosis of Autism Spectrum  
1220 Disorders. *J. Am. Acad. Child Adolesc. Psychiatry* **45**, 1094–1103 (2006).

1221 3. Loomes, R., Hull, L. & Mandy, W. P. L. What Is the Male-to-Female Ratio in Autism Spectrum  
1222 Disorder? A Systematic Review and Meta-Analysis. *J. Am. Acad. Child Adolesc. Psychiatry* **56**, 466–  
1223 474 (2017).

- 1224 4. Brugha, T. S. *et al.* Epidemiology of autism in adults across age groups and ability levels. *Br. J.*  
 1225 *Psychiatry* **209**, 498–503 (2016).
- 1226 5. Brugha, T., Bankart, J., McManus, S. & Gullon-Scott, F. CDC autism rate: misplaced reliance on  
 1227 passive sampling? *The Lancet* **392**, 732–733 (2018).
- 1228 6. Baxter, A. J. *et al.* The epidemiology and global burden of autism spectrum disorders. *Psychol.*  
 1229 *Med.* **45**, 601–613 (2014).
- 1230 7. Elsabbagh, M. *et al.* Global Prevalence of Autism and Other Pervasive Developmental Disorders:  
 1231 Global epidemiology of autism. *Autism Res.* **5**, 160–179 (2012).
- 1232 8. Magnusson, C. *et al.* Migration and autism spectrum disorder: population-based study. *Br. J.*  
 1233 *Psychiatry* **201**, 109–115 (2012).
- 1234 9. Goodman, R. & Richards, H. Child and Adolescent Psychiatric Presentations of Second-Generation  
 1235 Afro-Caribbeans in Britain. *Br. J. Psychiatry* **167**, 362–369 (1995).
- 1236 10. Dyches, T. T., Wilder, L. K., Sudweeks, R. R., Obiakor, F. E. & Algozzine, B. Multicultural Issues in  
 1237 Autism. *J. Autism Dev. Disord.* **34**, 211–222 (2004).
- 1238 11. Keen, D. V., Reid, F. D. & Arnone, D. Autism, ethnicity and maternal immigration. *Br. J. Psychiatry*  
 1239 **196**, 274–281 (2010).
- 1240 12. McManus S, Bebbington P, Jenkins R & Brugha T. *Mental Health and Wellbeing in England: Adult*  
 1241 *Psychiatric Morbidity Survey 2014.* (2016).
- 1242 13. James, S. L. *et al.* Global, regional, and national incidence, prevalence, and years lived with  
 1243 disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic  
 1244 analysis for the Global Burden of Disease Study 2017. *The Lancet* **392**, 1789–1858 (2018).
- 1245 14. Marcheselli, F & *et al.* *Mental health of children and young people in England, 2017: Autism*  
 1246 *spectrum, eating and other less common disorders.* (2018).
- 1247 15. Brugha, T. C & *et al.* *Autism spectrum disorder, adult psychiatric morbidity survey 2014.* (2014).

- 1248 16. Lundstrom, S., Reichenberg, A., Anckarsater, H., Lichtenstein, P. & Gillberg, C. Autism phenotype  
 1249 versus registered diagnosis in Swedish children: prevalence trends over 10 years in general  
 1250 population samples. *BMJ* **350**, h1961–h1961 (2015).
- 1251 17. Tromans, S., Chester, V., Kiani, R., Alexander, R. & Brugha, T. The Prevalence of Autism Spectrum  
 1252 Disorders in Adult Psychiatric Inpatients: A Systematic Review. *Clin. Pract. Epidemiol. Ment. Health*  
 1253 **14**, 177–187 (2018).
- 1254 18. Modabbernia, A., Velthorst, E. & Reichenberg, A. Environmental risk factors for autism: an  
 1255 evidence-based review of systematic reviews and meta-analyses. *Mol. Autism* **8**, (2017).
- 1256 19. Wu, S. *et al.* Advanced parental age and autism risk in children: a systematic review and meta-  
 1257 analysis. *Acta Psychiatr. Scand.* **135**, 29–41 (2016).
- 1258 20. Taylor, L. E., Swerdfeger, A. L. & Eslick, G. D. Vaccines are not associated with autism: An evidence-  
 1259 based meta-analysis of case-control and cohort studies. *Vaccine* **32**, 3623–3629 (2014).
- 1260 21. Lai, M.-C., Lombardo, M. V. & Baron-Cohen, S. Autism. *The Lancet* **383**, 896–910 (2014).
- 1261 22. Velikonja, T., Fett, A.-K. & Velthorst, E. Patterns of Nonsocial and Social Cognitive Functioning in  
 1262 Adults With Autism Spectrum Disorder: A Systematic Review and Meta-analysis. *JAMA Psychiatry*  
 1263 **76**, 135 (2019).
- 1264 23. McNally Keehn, R. H., Lincoln, A. J., Brown, M. Z. & Chavira, D. A. The Coping Cat Program for  
 1265 Children with Anxiety and Autism Spectrum Disorder: A Pilot Randomized Controlled Trial. *J.*  
 1266 *Autism Dev. Disord.* **43**, 57–67 (2013).
- 1267 24. Jones, E. J. H., Gliga, T., Bedford, R., Charman, T. & Johnson, M. H. Developmental pathways to  
 1268 autism: A review of prospective studies of infants at risk. *Neurosci. Biobehav. Rev.* **39**, 1–33 (2014).
- 1269 25. Ozonoff, S. *et al.* Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research  
 1270 Consortium Study. *PEDIATRICS* (2011) doi:10.1542/peds.2010-2825.

- 1271 26. Jones, R. M. & Lord, C. Diagnosing autism in neurobiological research studies. *Behav. Brain Res.*  
 1272 **251**, 113–124 (2013).
- 1273 27. Johnson, M. H. Autism: Demise of the Innate Social Orienting Hypothesis. *Curr. Biol.* **24**, R30–R31  
 1274 (2014).
- 1275 28. Johnson, M. H., Jones, E. J. H. & Gliga, T. Brain adaptation and alternative developmental  
 1276 trajectories. *Dev. Psychopathol.* **27**, 425–442 (2015).
- 1277 29. The Lancet Psychiatry. Of mice and mental health. *Lancet Psychiatry* **6**, 877 (2019).
- 1278 30. Nelson, C. A. *et al.* An integrative, multidisciplinary approach to the study of brain-behavior  
 1279 relations in the context of typical and atypical development. *Dev. Psychopathol.* **14**, 499–520  
 1280 (2002).
- 1281 31. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat.*  
 1282 *Genet.* **45**, 984–994 (2013).
- 1283 32. Gaugler, T. *et al.* Most genetic risk for autism resides with common variation. *Nat. Genet.* **46**, 881–  
 1284 885 (2014).
- 1285 33. Wang, K., Gaitsch, H., Poon, H., Cox, N. J. & Rzhetsky, A. Classification of common human diseases  
 1286 derived from shared genetic and environmental determinants. *Nat. Genet.* **49**, 1319–1325 (2017).
- 1287 34. Sanders, S. J. *et al.* Insights into Autism Spectrum Disorder Genomic Architecture and Biology from  
 1288 71 Risk Loci. *Neuron* **87**, 1215–1233 (2015).
- 1289 35. Satterstrom, F. K. *et al.* Large-scale exome sequencing study implicates both developmental and  
 1290 functional changes in the neurobiology of autism. *bioRxiv* (2019) doi:10.1101/484113.
- 1291 36. Sanders, S. J. *et al.* De novo mutations revealed by whole-exome sequencing are strongly  
 1292 associated with autism. *Nature* **485**, 237–241 (2012).
- 1293 37. Neale, B. M. *et al.* Patterns and rates of exonic de novo mutations in autism spectrum disorders.  
 1294 *Nature* **485**, 242–245 (2012).

- 1295 38. O’Roak, B. J. *et al.* Sporadic autism exomes reveal a highly interconnected protein network of de  
1296 novo mutations. *Nature* **485**, 246–250 (2012).
- 1297 39. Sanders, S. J. *et al.* Multiple Recurrent De Novo CNVs, Including Duplications of the 7q11.23  
1298 Williams Syndrome Region, Are Strongly Associated with Autism. *Neuron* **70**, 863–885 (2011).
- 1299 40. Levy, D. *et al.* Rare De Novo and Transmitted Copy-Number Variation in Autistic Spectrum  
1300 Disorders. *Neuron* **70**, 886–897 (2011).
- 1301 41. Sebat, J. *et al.* Strong Association of De Novo Copy Number Mutations with Autism. *Science* **316**,  
1302 445–449 (2007).
- 1303 42. Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium *et al.*  
1304 Identification of common genetic risk variants for autism spectrum disorder. *Nat. Genet.* **51**, 431–  
1305 444 (2019).
- 1306 43. Willsey, J. *et al.* De Novo Coding Variants Are Strongly Associated with Tourette Syndrome. *Eur.*  
1307 *Neuropsychopharmacol.* **29**, S737 (2019).
- 1308 44. Epi4K: Gene discovery in 4,000 genomes. *Epilepsia* **53**, 1457–1467 (2012).
- 1309 45. Paris Autism Research International Sibpair Study *et al.* Mutations of the X-linked genes encoding  
1310 neuroligins NLGN3 and NLGN4 are associated with autism. *Nat. Genet.* **34**, 27–29 (2003).
- 1311 46. Iossifov, I. *et al.* The contribution of de novo coding mutations to autism spectrum disorder.  
1312 *Nature* **515**, 216–221 (2014).
- 1313 47. The DDD Study *et al.* Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*  
1314 **515**, 209–215 (2014).
- 1315 48. Sestan, N. & State, M. W. Lost in Translation: Traversing the Complex Path from Genomics to  
1316 Therapeutics in Autism Spectrum Disorder. *Neuron* **100**, 406–423 (2018).
- 1317 49. State, M. W. & Sestan, N. The Emerging Biology of Autism Spectrum Disorders. *Science* **337**, 1301–  
1318 1303 (2012).

- 1319 50. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427 (2014).
- 1320 51. Devlin, B. & Scherer, S. W. Genetic architecture in autism spectrum disorder. *Curr. Opin. Genet.*  
1321 *Dev.* **22**, 229–237 (2012).
- 1322 52. de la Torre-Ubieta, L., Won, H., Stein, J. L. & Geschwind, D. H. Advancing the understanding of  
1323 autism disease mechanisms through genetics. *Nat. Med.* **22**, 345–361 (2016).
- 1324 53. *SFARI Gene Website*. <https://gene.sfari.org/>.
- 1325 54. Parikshak, N. N. *et al.* Integrative Functional Genomic Analyses Implicate Specific Molecular  
1326 Pathways and Circuits in Autism. *Cell* **155**, 1008–1021 (2013).
- 1327 55. Ben-David, E. & Shifman, S. Combined analysis of exome sequencing points toward a major role for  
1328 transcription regulation during brain development in autism. *Mol. Psychiatry* **18**, 1054–1056  
1329 (2012).
- 1330 56. Willsey, A. J. *et al.* Coexpression Networks Implicate Human Midfetal Deep Cortical Projection  
1331 Neurons in the Pathogenesis of Autism. *Cell* **155**, 997–1007 (2013).
- 1332 57. Pinto, D. *et al.* Functional impact of global rare copy number variation in autism spectrum  
1333 disorders. *Nature* **466**, 368–372 (2010).
- 1334 58. Gilman, S. R. *et al.* Rare De Novo Variants Associated with Autism Implicate a Large Functional  
1335 Network of Genes Involved in Formation and Function of Synapses. *Neuron* **70**, 898–907 (2011).
- 1336 59. Fuccillo, M. V. Striatal Circuits as a Common Node for Autism Pathophysiology. *Front. Neurosci.* **10**,  
1337 (2016).
- 1338 60. Velmeshev, D. *et al.* Single-cell genomics identifies cell type–specific molecular changes in autism.  
1339 *Science* **364**, 685–689 (2019).
- 1340 61. Power, J. D. *et al.* Customized head molds reduce motion during resting state fMRI scans.  
1341 *NeuroImage* **189**, 141–149 (2019).

- 1342 62. Solso, S. *et al.* Diffusion Tensor Imaging Provides Evidence of Possible Axonal Overconnectivity in  
1343 Frontal Lobes in Autism Spectrum Disorder Toddlers. *Biol. Psychiatry* **79**, 676–684 (2016).
- 1344 63. Clements, C. C. *et al.* Evaluation of the Social Motivation Hypothesis of Autism. *JAMA Psychiatry*  
1345 **75**, 797 (2018).
- 1346 64. Ecker, C. Brain Anatomy and Its Relationship to Behavior in Adults With Autism Spectrum Disorder.  
1347 *Arch. Gen. Psychiatry* **69**, 195 (2012).
- 1348 65. Langen, M. *et al.* Changes in the Development of Striatum Are Involved in Repetitive Behavior in  
1349 Autism. *Biol. Psychiatry* **76**, 405–411 (2014).
- 1350 66. Elsabbagh, M. & Johnson, M. H. Autism and the Social Brain: The First-Year Puzzle. *Biol. Psychiatry*  
1351 **80**, 94–99 (2016).
- 1352 67. Courchesne, E. *et al.* Unusual brain growth patterns in early life in patients with autistic disorder:  
1353 An MRI study. *Neurology* **57**, 245–254 (2001).
- 1354 68. Hazlett, H. C. *et al.* Magnetic Resonance Imaging and Head Circumference Study of Brain Size in  
1355 Autism. *Arch. Gen. Psychiatry* **62**, 1366 (2005).
- 1356 69. Wolff, J. J. *et al.* Differences in White Matter Fiber Tract Development Present From 6 to 24  
1357 Months in Infants With Autism. *Am. J. Psychiatry* **169**, 589–600 (2012).
- 1358 70. Hazlett, H. C. *et al.* Early brain development in infants at high risk for autism spectrum disorder.  
1359 *Nature* **542**, 348–351 (2017).
- 1360 71. Wolff, J. J. *et al.* Neural circuitry at age 6 months associated with later repetitive behavior and  
1361 sensory responsiveness in autism. *Mol. Autism* **8**, (2017).
- 1362 72. Emerson, R. W. *et al.* Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis  
1363 of autism at 24 months of age. *Sci. Transl. Med.* **9**, eaag2882 (2017).
- 1364 73. Smith, E. *et al.* Cortical thickness change in autism during early childhood: CT in Early Childhood  
1365 ASD. *Hum. Brain Mapp.* **37**, 2616–2629 (2016).

- 1366 74. Uddin, L. Q., Dajani, D. R., Voorhies, W., Bednarz, H. & Kana, R. K. Progress and roadblocks in the  
 1367 search for brain-based biomarkers of autism and attention-deficit/hyperactivity disorder. *Transl.*  
 1368 *Psychiatry* **7**, e1218–e1218 (2017).
- 1369 75. Herringshaw, A. J., Ammons, C. J., DeRamus, T. P. & Kana, R. K. Hemispheric differences in  
 1370 language processing in autism spectrum disorders: A meta-analysis of neuroimaging studies.  
 1371 *Autism Res.* **9**, 1046–1057 (2016).
- 1372 76. He, Y., Byrge, L. & Kennedy, D. P. Non-replication of functional connectivity differences in autism  
 1373 spectrum disorder across multiple sites and denoising strategies. *bioRxiv* (2019)  
 1374 doi:10.1101/640797.
- 1375 77. Lawrence, K. E., Hernandez, L. M., Bookheimer, S. Y. & Dapretto, M. Atypical longitudinal  
 1376 development of functional connectivity in adolescents with autism spectrum disorder. *Autism Res.*  
 1377 **12**, 53–65 (2018).
- 1378 78. Plitt, M., Barnes, K. A., Wallace, G. L., Kenworthy, L. & Martin, A. Resting-state functional  
 1379 connectivity predicts longitudinal change in autistic traits and adaptive functioning in autism. *Proc.*  
 1380 *Natl. Acad. Sci.* **112**, E6699–E6706 (2015).
- 1381 79. Di Martino, A. *et al.* The autism brain imaging data exchange: towards a large-scale evaluation of  
 1382 the intrinsic brain architecture in autism. *Mol. Psychiatry* **19**, 659–667 (2013).
- 1383 80. Doyle-Thomas, K. A. R. *et al.* Atypical functional brain connectivity during rest in autism spectrum  
 1384 disorders. *Ann. Neurol.* **77**, 866–876 (2015).
- 1385 81. Supekar, K. *et al.* Brain Hyperconnectivity in Children with Autism and its Links to Social Deficits.  
 1386 *Cell Rep.* **5**, 738–747 (2013).
- 1387 82. Dajani, D. R. & Uddin, L. Q. Local brain connectivity across development in autism spectrum  
 1388 disorder: A cross-sectional investigation. *Autism Res.* **9**, 43–54 (2015).



- 1389 83. Hull, J. V. *et al.* Resting-State Functional Connectivity in Autism Spectrum Disorders: A Review.  
1390 *Front. Psychiatry* **7**, (2017).
- 1391 84. Lombardo, M. V. *et al.* Different Functional Neural Substrates for Good and Poor Language  
1392 Outcome in Autism. *Neuron* **86**, 567–577 (2015).
- 1393 85. Carlisi, C. O. *et al.* Disorder-Specific and Shared Brain Abnormalities During Vigilance in Autism and  
1394 Obsessive-Compulsive Disorder. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* **2**, 644–654 (2017).
- 1395 86. Alaerts, K., Swinnen, S. P. & Wenderoth, N. Sex differences in autism: a resting-state fMRI  
1396 investigation of functional brain connectivity in males and females. *Soc. Cogn. Affect. Neurosci.* **11**,  
1397 1002–1016 (2016).
- 1398 87. Kirkovski, M., Enticott, P. G., Hughes, M. E., Rossell, S. L. & Fitzgerald, P. B. Atypical Neural Activity  
1399 in Males But Not Females with Autism Spectrum Disorder. *J. Autism Dev. Disord.* **46**, 954–963  
1400 (2016).
- 1401 88. Venkataraman, A. *et al.* Pivotal response treatment prompts a functional rewiring of the brain  
1402 among individuals with autism spectrum disorder. *NeuroReport* **27**, 1081–1085 (2016).
- 1403 89. Levisohn, P. M. The autism-epilepsy connection. *Epilepsia* **48**, 33–35 (2007).
- 1404 90. Cantor, D. S., Thatcher, R. W., Hrybyk, M. & Kaye, H. Computerized EEG analyses of autistic  
1405 children. *J. Autism Dev. Disord.* **16**, 169–187 (1986).
- 1406 91. Lefebvre, A. *et al.* Alpha Waves as a Neuromarker of Autism Spectrum Disorder: The Challenge of  
1407 Reproducibility and Heterogeneity. *Front. Neurosci.* **12**, (2018).
- 1408 92. Tierney, A. L., Gabard-Durnam, L., Vogel-Farley, V., Tager-Flusberg, H. & Nelson, C. A.  
1409 Developmental Trajectories of Resting EEG Power: An Endophenotype of Autism Spectrum  
1410 Disorder. *PLoS ONE* **7**, e39127 (2012).
- 1411 93. Oberman, L. M. *et al.* EEG evidence for mirror neuron dysfunction in autism spectrum disorders.  
1412 *Cogn. Brain Res.* **24**, 190–198 (2005).

- 1413 94. Fan, Y.-T., Decety, J., Yang, C.-Y., Liu, J.-L. & Cheng, Y. Unbroken mirror neurons in autism spectrum  
1414 disorders. *J. Child Psychol. Psychiatry* **51**, 981–988 (2010).
- 1415 95. Southgate, V. & de C. Hamilton, A. F. Unbroken mirrors: challenging a theory of Autism. *Trends*  
1416 *Cogn. Sci.* **12**, 225–229 (2008).
- 1417 96. Bernier, R., Aaronson, B. & McPartland, J. The role of imitation in the observed heterogeneity in  
1418 EEG mu rhythm in autism and typical development. *Brain Cogn.* **82**, 69–75 (2013).
- 1419 97. Raymaekers, R., Wiersema, J. R. & Roeyers, H. EEG study of the mirror neuron system in children  
1420 with high functioning autism. *Brain Res.* **1304**, 113–121 (2009).
- 1421 98. Dumas, G., Soussignan, R., Hugueville, L., Martinerie, J. & Nadel, J. Revisiting mu suppression in  
1422 autism spectrum disorder. *Brain Res.* **1585**, 108–119 (2014).
- 1423 99. MARCO, E. J., HINKLEY, L. B. N., HILL, S. S. & NAGARAJAN, S. S. Sensory Processing in Autism: A  
1424 Review of Neurophysiologic Findings. *Pediatr. Res.* **69**, 48R–54R (2011).
- 1425 100. Schwartz, S., Shinn-Cunningham, B. & Tager-Flusberg, H. Meta-analysis and systematic review of  
1426 the literature characterizing auditory mismatch negativity in individuals with autism. *Neurosci.*  
1427 *Biobehav. Rev.* **87**, 106–117 (2018).
- 1428 101. Kang, E. *et al.* Atypicality of the N170 Event-Related Potential in Autism Spectrum Disorder: A  
1429 Meta-analysis. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* **3**, 657–666 (2018).
- 1430 102. Bonnet-Brilhault, F. *et al.* GABA/Glutamate synaptic pathways targeted by integrative genomic and  
1431 electrophysiological explorations distinguish autism from intellectual disability. *Mol. Psychiatry* **21**,  
1432 411–418 (2015).
- 1433 103. Schilbach, L. Towards a second-person neuropsychiatry. *Philos. Trans. R. Soc. B Biol. Sci.* **371**,  
1434 20150081 (2016).
- 1435 104. Barraza, P. *et al.* Implementing EEG hyperscanning setups. *MethodsX* **6**, 428–436 (2019).

- 1436 105. Dumas, G., de Guzman, G. C., Tognoli, E. & Kelso, J. A. S. The human dynamic clamp as a paradigm  
1437 for social interaction. *Proc. Natl. Acad. Sci.* **111**, E3726–E3734 (2014).
- 1438 106. Jones, E. J. H. *et al.* Reduced engagement with social stimuli in 6-month-old infants with later  
1439 autism spectrum disorder: a longitudinal prospective study of infants at high familial risk. *J.*  
1440 *Neurodev. Disord.* **8**, (2016).
- 1441 107. Ciarrusta, J. *et al.* Social Brain Functional Maturation in Newborn Infants With and Without a  
1442 Family History of Autism Spectrum Disorder. *JAMA Netw. Open* **2**, e191868 (2019).
- 1443 108. Levin, A. R., Varcin, K. J., O’Leary, H. M., Tager-Flusberg, H. & Nelson, C. A. EEG power at 3 months  
1444 in infants at high familial risk for autism. *J. Neurodev. Disord.* **9**, (2017).
- 1445 109. Kolesnik, A. *et al.* Increased cortical reactivity to repeated tones at 8 months in infants with later  
1446 ASD. *Transl. Psychiatry* **9**, (2019).
- 1447 110. Rippon, G., Brock, J., Brown, C. & Boucher, J. Disordered connectivity in the autistic brain:  
1448 Challenges for the ‘new psychophysiology’. *Int. J. Psychophysiol.* **63**, 164–172 (2007).
- 1449 111. Rosenberg, A., Patterson, J. S. & Angelaki, D. E. A computational perspective on autism. *Proc. Natl.*  
1450 *Acad. Sci.* **112**, 9158–9165 (2015).
- 1451 112. Masuda, F. *et al.* Motor cortex excitability and inhibitory imbalance in autism spectrum disorder  
1452 assessed with transcranial magnetic stimulation: a systematic review. *Transl. Psychiatry* **9**, (2019).
- 1453 113. O’Reilly, C., Lewis, J. D. & Elsabbagh, M. Is functional brain connectivity atypical in autism? A  
1454 systematic review of EEG and MEG studies. *PLOS ONE* **12**, e0175870 (2017).
- 1455 114. Khan, S. *et al.* Somatosensory cortex functional connectivity abnormalities in autism show opposite  
1456 trends, depending on direction and spatial scale. *Brain* **138**, 1394–1409 (2015).
- 1457 115. Chen, H., Nomi, J. S., Uddin, L. Q., Duan, X. & Chen, H. Intrinsic functional connectivity variance and  
1458 state-specific under-connectivity in autism. *Hum. Brain Mapp.* **38**, 5740–5755 (2017).

- 1459 116. Catarino, A., Churches, O., Baron-Cohen, S., Andrade, A. & Ring, H. Atypical EEG complexity in  
 1460 autism spectrum conditions: A multiscale entropy analysis. *Clin. Neurophysiol.* **122**, 2375–2383  
 1461 (2011).
- 1462 117. Engemann, D. A. *et al.* Robust EEG-based cross-site and cross-protocol classification of states of  
 1463 consciousness. *Brain* **141**, 3179–3192 (2018).
- 1464 118. Estimating the reproducibility of psychological science. *Science* **349**, aac4716–aac4716 (2015).
- 1465 119. Lord, C *et al.* *Autism diagnostic observation schedule: ADOS-2*. (2012).
- 1466 120. Regier, D. A. *et al.* DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability  
 1467 of Selected Categorical Diagnoses. *Am. J. Psychiatry* **170**, 59–70 (2013).
- 1468 121. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth*  
 1469 *Edition*. (American Psychiatric Association, 2013).
- 1470 122. WHO. *International classification of diseases for mortality and morbidity statistics (11th Revision)*.  
 1471 <https://icd.who.int/browse11/l-m/en> (2018).
- 1472 123. Constantino, J. N. & Charman, T. Diagnosis of autism spectrum disorder: reconciling the syndrome,  
 1473 its diverse origins, and variation in expression. *Lancet Neurol.* **15**, 279–291 (2016).
- 1474 124. Lord, C. A Multisite Study of the Clinical Diagnosis of Different Autism Spectrum Disorders. *Arch.*  
 1475 *Gen. Psychiatry* **69**, 306 (2012).
- 1476 125. Miller, J. N. & Ozonoff, S. The external validity of Asperger disorder: lack of evidence from the  
 1477 domain of neuropsychology. *J. Abnorm. Psychol.* **109**, 227–238 (2000).
- 1478 126. Green, D., Chandler, S., Charman, T., Simonoff, E. & Baird, G. Brief Report: DSM-5 Sensory  
 1479 Behaviours in Children With and Without an Autism Spectrum Disorder. *J. Autism Dev. Disord.* **46**,  
 1480 3597–3606 (2016).
- 1481 127. Ozonoff, S. *et al.* Diagnosis of Autism Spectrum Disorder After Age 5 in Children Evaluated  
 1482 Longitudinally Since Infancy. *J. Am. Acad. Child Adolesc. Psychiatry* **57**, 849–857.e2 (2018).

- 1483 128. Russell, G., Steer, C. & Golding, J. Social and demographic factors that influence the diagnosis of  
1484 autistic spectrum disorders. *Soc. Psychiatry Psychiatr. Epidemiol.* **46**, 1283–1293 (2010).
- 1485 129. Charman, T. & Gotham, K. Measurement Issues: Screening and diagnostic instruments for autism  
1486 spectrum disorders - lessons from research and practise. *Child Adolesc. Ment. Health* **18**, 52–63  
1487 (2012).
- 1488 130. Ashwood, K. L., Buitelaar, J., Murphy, D., Spooren, W. & Charman, T. European clinical network:  
1489 autism spectrum disorder assessments and patient characterisation. *Eur. Child Adolesc. Psychiatry*  
1490 **24**, 985–995 (2015).
- 1491 131. Rutter, M, LeCouteur, A & Lord, C. *Autism diagnostic interview-revised (ADI-R)*. (Western  
1492 Psychological Services, 2003).
- 1493 132. Durkin, M. S. *et al.* Autism screening and diagnosis in low resource settings: Challenges and  
1494 opportunities to enhance research and services worldwide. *Autism Res.* **8**, 473–476 (2015).
- 1495 133. Baird, G. *et al.* Prevalence of disorders of the autism spectrum in a population cohort of children in  
1496 South Thames: the Special Needs and Autism Project (SNAP). *The Lancet* **368**, 210–215 (2006).
- 1497 134. Luyster, R. *et al.* The Autism Diagnostic Observation Schedule—Toddler Module: A New Module of  
1498 a Standardized Diagnostic Measure for Autism Spectrum Disorders. *J. Autism Dev. Disord.* **39**,  
1499 1305–1320 (2009).
- 1500 135. de Vries, P. J. Thinking globally to meet local needs. *Curr. Opin. Neurol.* **29**, 130–136 (2016).
- 1501 136. Georgiades, S., Bishop, S. L. & Frazier, T. Editorial Perspective: Longitudinal research in autism -  
1502 introducing the concept of ‘chronogeneity’. *J. Child Psychol. Psychiatry* **58**, 634–636 (2017).
- 1503 137. Fountain, C., Winter, A. S. & Bearman, P. S. Six Developmental Trajectories Characterize Children  
1504 With Autism. *PEDIATRICS* **129**, e1112–e1120 (2012).
- 1505 138. Kim, S. H. *et al.* Variability in Autism Symptom Trajectories Using Repeated Observations From 14  
1506 to 36 Months of Age. *J. Am. Acad. Child Adolesc. Psychiatry* **57**, 837-848.e2 (2018).

- 1507 139. Bussu, G., Jones, E. J. H., Charman, T., Johnson, M. H. & Buitelaar, J. K. Latent trajectories of  
 1508 adaptive behaviour in infants at high and low familial risk for autism spectrum disorder. *Mol.*  
 1509 *Autism* **10**, (2019).
- 1510 140. Zerbi, V. *et al.* Dysfunctional Autism Risk Genes Cause Circuit-Specific Connectivity Deficits With  
 1511 Distinct Developmental Trajectories. *Cereb. Cortex* **28**, 2495–2506 (2018).
- 1512 141. Fein, D. *et al.* Optimal outcome in individuals with a history of autism. *J. Child Psychol. Psychiatry*  
 1513 **54**, 195–205 (2013).
- 1514 142. Anderson, D. K., Liang, J. W. & Lord, C. Predicting young adult outcome among more and less  
 1515 cognitively able individuals with autism spectrum disorders. *J. Child Psychol. Psychiatry* **55**, 485–  
 1516 494 (2013).
- 1517 143. Chlebowski, C., Robins, D. L., Barton, M. L. & Fein, D. Large-Scale Use of the Modified Checklist for  
 1518 Autism in Low-Risk Toddlers. *PEDIATRICS* **131**, e1121–e1127 (2013).
- 1519 144. Stenberg, N. *et al.* Identifying Children with Autism Spectrum Disorder at 18 Months in a General  
 1520 Population Sample. *Paediatr. Perinat. Epidemiol.* **28**, 255–262 (2014).
- 1521 145. Pierce, K., Courchesne, E. & Bacon, E. To Screen or Not to Screen Universally for Autism is not the  
 1522 Question: Why the Task Force Got It Wrong. *J. Pediatr.* **176**, 182–194 (2016).
- 1523 146. Siu, A. L. *et al.* Screening for Autism Spectrum Disorder in Young Children: US Preventive Services  
 1524 Task Force Recommendation Statement. *JAMA* **315**, 691 (2016).
- 1525 147. Øien, R. A. *et al.* Clinical Features of Children With Autism Who Passed 18-Month Screening.  
 1526 *Pediatrics* **141**, e20173596 (2018).
- 1527 148. Sánchez-García, A. B., Galindo-Villardón, P., Nieto-Librero, A. B., Martín-Rodero, H. & Robins, D. L.  
 1528 Toddler Screening for Autism Spectrum Disorder: A Meta-Analysis of Diagnostic Accuracy. *J. Autism*  
 1529 *Dev. Disord.* **49**, 1837–1852 (2019).

- 1530 149. Marlow, M., Servili, C. & Tomlinson, M. A review of screening tools for the identification of autism  
 1531 spectrum disorders and developmental delay in infants and young children: recommendations for  
 1532 use in low- and middle-income countries. *Autism Res.* **12**, 176–199 (2019).
- 1533 150. Raza, S. *et al.* Brief Report: Evaluation of the Short Quantitative Checklist for Autism in Toddlers (Q-  
 1534 CHAT-10) as a Brief Screen for Autism Spectrum Disorder in a High-Risk Sibling Cohort. *J. Autism*  
 1535 *Dev. Disord.* **49**, 2210–2218 (2019).
- 1536 151. Charman, T. *et al.* Testing two screening instruments for autism spectrum disorder in UK  
 1537 community child health services. *Dev. Med. Child Neurol.* **58**, 369–375 (2015).
- 1538 152. Brett, D., Warnell, F., McConachie, H. & Parr, J. R. Factors Affecting Age at ASD Diagnosis in UK: No  
 1539 Evidence that Diagnosis Age has Decreased Between 2004 and 2014. *J. Autism Dev. Disord.* **46**,  
 1540 1974–1984 (2016).
- 1541 153. Zuckerman, K. E., Lindly, O. J. & Sinche, B. K. Parental Concerns, Provider Response, and Timeliness  
 1542 of Autism Spectrum Disorder Diagnosis. *J. Pediatr.* **166**, 1431-1439.e1 (2015).
- 1543 154. Boterberg, S., Charman, T., Marschik, P. B., Bölte, S. & Roeyers, H. Regression in autism spectrum  
 1544 disorder: A critical overview of retrospective findings and recommendations for future research.  
 1545 *Neurosci. Biobehav. Rev.* **102**, 24–55 (2019).
- 1546 155. Pearson, N., Charman, T., Happé, F., Bolton, P. F. & McEwen, F. S. Regression in autism spectrum  
 1547 disorder: Reconciling findings from retrospective and prospective research. *Autism Res.* **11**, 1602–  
 1548 1620 (2018).
- 1549 156. Ozonoff, S. & Iosif, A.-M. Changing conceptualizations of regression: What prospective studies  
 1550 reveal about the onset of autism spectrum disorder. *Neurosci. Biobehav. Rev.* **100**, 296–304 (2019).
- 1551 157. Brugha, T. S. *et al.* Validating two survey methods for identifying cases of autism spectrum disorder  
 1552 among adults in the community. *Psychol. Med.* **42**, 647–656 (2011).

- 1553 158. Brugha, T. S. The Psychiatry of Adult Autism and Asperger Syndrome. *Oxf. Med. Online* (2018)  
 1554 doi:10.1093/med/9780198796343.001.0001.
- 1555 159. Epstein, J., Johnson, D. E. & Conners, C. K. Conners' Adult ADHD Diagnostic Interview for DSM-IV™.  
 1556 (2012) doi:10.1037/t04960-000.
- 1557 160. Lai, M.-C. *et al.* Prevalence of co-occurring mental health diagnoses in the autism population: a  
 1558 systematic review and meta-analysis. *Lancet Psychiatry* **6**, 819–829 (2019).
- 1559 161. Havdahl, A. & Bishop, S. Heterogeneity in prevalence of co-occurring psychiatric conditions in  
 1560 autism. *Lancet Psychiatry* **6**, 794–795 (2019).
- 1561 162. Croen, L. A. *et al.* The health status of adults on the autism spectrum. *Autism* **19**, 814–823 (2015).
- 1562 163. Mannion, A., Leader, G. & Healy, O. An investigation of comorbid psychological disorders, sleep  
 1563 problems, gastrointestinal symptoms and epilepsy in children and adolescents with Autism  
 1564 Spectrum Disorder. *Res. Autism Spectr. Disord.* **7**, 35–42 (2013).
- 1565 164. Soke, G. N., Maenner, M. J., Christensen, D., Kurzius-Spencer, M. & Schieve, L. A. Prevalence of Co-  
 1566 occurring Medical and Behavioral Conditions/Symptoms Among 4- and 8-Year-Old Children with  
 1567 Autism Spectrum Disorder in Selected Areas of the United States in 2010. *J. Autism Dev. Disord.* **48**,  
 1568 2663–2676 (2018).
- 1569 165. Chandler, S. *et al.* Emotional and behavioural problems in young children with autism spectrum  
 1570 disorder. *Dev. Med. Child Neurol.* **58**, 202–208 (2016).
- 1571 166. Pezzimenti, F., Han, G. T., Vasa, R. A. & Gotham, K. Depression in Youth with Autism Spectrum  
 1572 Disorder. *Child Adolesc. Psychiatr. Clin. N. Am.* **28**, 397–409 (2019).
- 1573 167. Hwang, Y. I. (Jane), Srasuebkul, P., Foley, K., Arnold, S. & Trollor, J. N. Mortality and cause of death  
 1574 of Australians on the autism spectrum. *Autism Res.* **12**, 806–815 (2019).
- 1575 168. Hirvikoski, T. *et al.* Premature mortality in autism spectrum disorder. *Br. J. Psychiatry* **208**, 232–238  
 1576 (2016).



- 1577 169. Havdahl, K. A. *et al.* Multidimensional Influences on Autism Symptom Measures: Implications for  
1578 Use in Etiological Research. *J. Am. Acad. Child Adolesc. Psychiatry* **55**, 1054-1063.e3 (2016).
- 1579 170. Nicolaidis, C. *et al.* Comparison of healthcare experiences in autistic and non-autistic adults: a  
1580 cross-sectional online survey facilitated by an academic-community partnership. *J. Gen. Intern.*  
1581 *Med.* **28**, 761–769 (2013).
- 1582 171. Schreibman, L. *et al.* Naturalistic Developmental Behavioral Interventions: Empirically Validated  
1583 Treatments for Autism Spectrum Disorder. *J. Autism Dev. Disord.* **45**, 2411–2428 (2015).
- 1584 172. Tomlinson, M. *et al.* Setting global research priorities for developmental disabilities, including  
1585 intellectual disabilities and autism: Setting research priorities for developmental disabilities. *J.*  
1586 *Intellect. Disabil. Res.* **58**, 1121–1130 (2014).
- 1587 173. Rahman, A. *et al.* Effectiveness of the parent-mediated intervention for children with autism  
1588 spectrum disorder in south Asia in India and Pakistan (PASS): a randomised controlled trial. *Lancet*  
1589 *Psychiatry* **3**, 128–136 (2016).
- 1590 174. Lovaas, O. I. Behavioral treatment and normal educational and intellectual functioning in young  
1591 autistic children. *J. Consult. Clin. Psychol.* **55**, 3–9 (1987).
- 1592 175. Nevill, R. E., Lecavalier, L. & Stratis, E. A. Meta-analysis of parent-mediated interventions for young  
1593 children with autism spectrum disorder. *Autism Int. J. Res. Pract.* **22**, 84–98 (2018).
- 1594 176. Kasari, C. *et al.* Randomized controlled trial of parental responsiveness intervention for toddlers at  
1595 high risk for autism. *Infant Behav. Dev.* **37**, 711–721 (2014).
- 1596 177. Shire, S. Y. *et al.* Hybrid implementation model of community-partnered early intervention for  
1597 toddlers with autism: a randomized trial. *J. Child Psychol. Psychiatry* **58**, 612–622 (2016).
- 1598 178. Siller, M., Hutman, T. & Sigman, M. A Parent-Mediated Intervention to Increase Responsive  
1599 Parental Behaviors and Child Communication in Children with ASD: A Randomized Clinical Trial. *J.*  
1600 *Autism Dev. Disord.* **43**, 540–555 (2013).

- 1601 179. Rogers, S. J. *et al.* Effects of a Brief Early Start Denver Model (ESDM)–Based Parent Intervention on  
 1602 Toddlers at Risk for Autism Spectrum Disorders: A Randomized Controlled Trial. *J. Am. Acad. Child*  
 1603 *Adolesc. Psychiatry* **51**, 1052–1065 (2012).
- 1604 180. Green, J. *et al.* Parent-mediated communication-focused treatment in children with autism (PACT):  
 1605 a randomised controlled trial. *The Lancet* **375**, 2152–2160 (2010).
- 1606 181. Pickles, A. *et al.* Parent-mediated social communication therapy for young children with autism  
 1607 (PACT): long-term follow-up of a randomised controlled trial. *The Lancet* **388**, 2501–2509 (2016).
- 1608 182. Dawson, G. *et al.* Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The  
 1609 Early Start Denver Model. *PEDIATRICS* **125**, e17–e23 (2009).
- 1610 183. Charman, T. Editorial: Trials and Tribulations in Early Autism Intervention Research. *J. Am. Acad.*  
 1611 *Child Adolesc. Psychiatry* (2019) doi:10.1016/j.jaac.2019.03.004.
- 1612 184. Dawson, G. *et al.* Early Behavioral Intervention Is Associated With Normalized Brain Activity in  
 1613 Young Children With Autism. *J. Am. Acad. Child Adolesc. Psychiatry* **51**, 1150–1159 (2012).
- 1614 185. Myers, S. M., Johnson, C. P. & the Council on Children With Disabilities. Management of Children  
 1615 With Autism Spectrum Disorders. *PEDIATRICS* **120**, 1162–1182 (2007).
- 1616 186. Laugeson, E. A., Frankel, F., Gantman, A., Dillon, A. R. & Mogil, C. Evidence-Based Social Skills  
 1617 Training for Adolescents with Autism Spectrum Disorders: The UCLA PEERS Program. *J. Autism Dev.*  
 1618 *Disord.* **42**, 1025–1036 (2011).
- 1619 187. Reichow, B., Servili, C., Yasamy, M. T., Barbui, C. & Saxena, S. Non-Specialist Psychosocial  
 1620 Interventions for Children and Adolescents with Intellectual Disability or Lower-Functioning Autism  
 1621 Spectrum Disorders: A Systematic Review. *PLoS Med.* **10**, e1001572 (2013).
- 1622 188. Brignell, A. *et al.* Communication interventions for autism spectrum disorder in minimally verbal  
 1623 children. *Cochrane Database Syst. Rev.* (2018) doi:10.1002/14651858.CD012324.pub2.

- 1624 189. Tarver, J. *et al.* Child and parent outcomes following parent interventions for child emotional and  
1625 behavioral problems in autism spectrum disorders: A systematic review and meta-analysis. *Autism*  
1626 **23**, 1630–1644 (2019).
- 1627 190. Keefer, A. *et al.* Exploring Relationships Between Negative Cognitions and Anxiety Symptoms in  
1628 Youth With Autism Spectrum Disorder. *Behav. Ther.* **49**, 730–740 (2018).
- 1629 191. Bearss, K. *et al.* Effect of Parent Training vs Parent Education on Behavioral Problems in Children  
1630 With Autism Spectrum Disorder. *JAMA* **313**, 1524 (2015).
- 1631 192. Da Paz, N. S. & Wallander, J. L. Interventions that target improvements in mental health for  
1632 parents of children with autism spectrum disorders: A narrative review. *Clin. Psychol. Rev.* **51**, 1–14  
1633 (2017).
- 1634 193. Kasari, C. *et al.* Children with autism spectrum disorder and social skills groups at school: a  
1635 randomized trial comparing intervention approach and peer composition. *J. Child Psychol.*  
1636 *Psychiatry* **57**, 171–179 (2016).
- 1637 194. Marshall, D. *et al.* Social Stories in mainstream schools for children with autism spectrum disorder:  
1638 a feasibility randomised controlled trial. *BMJ Open* **6**, e011748 (2016).
- 1639 195. Taylor, J. L. *et al.* A Systematic Review of Vocational Interventions for Young Adults With Autism  
1640 Spectrum Disorders. *PEDIATRICS* **130**, 531–538 (2012).
- 1641 196. Pallathra, A. A., Cordero, L., Wong, K. & Brodtkin, E. S. Psychosocial Interventions Targeting Social  
1642 Functioning in Adults on the Autism Spectrum: a Literature Review. *Curr. Psychiatry Rep.* **21**,  
1643 (2019).
- 1644 197. White, S. W. *et al.* Psychosocial Treatments Targeting Anxiety and Depression in Adolescents and  
1645 Adults on the Autism Spectrum: Review of the Latest Research and Recommended Future  
1646 Directions. *Curr. Psychiatry Rep.* **20**, (2018).

- 1647 198. Shattuck, P. T., Wagner, M., Narendorf, S., Sterzing, P. & Hensley, M. Post–High School Service Use  
1648 Among Young Adults With an Autism Spectrum Disorder. *Arch. Pediatr. Adolesc. Med.* **165**, (2011).
- 1649 199. Wehman, P. *et al.* Effects of an employer-based intervention on employment outcomes for youth  
1650 with significant support needs due to autism. *Autism* **21**, 276–290 (2016).
- 1651 200. McCracken, J. T. *et al.* Risperidone in Children with Autism and Serious Behavioral Problems. *N.*  
1652 *Engl. J. Med.* **347**, 314–321 (2002).
- 1653 201. Owen, R. *et al.* Aripiprazole in the Treatment of Irritability in Children and Adolescents With  
1654 Autistic Disorder. *PEDIATRICS* **124**, 1533–1540 (2009).
- 1655 202. McPheeters, M. L. *et al.* A Systematic Review of Medical Treatments for Children With Autism  
1656 Spectrum Disorders. *PEDIATRICS* **127**, e1312–e1321 (2011).
- 1657 203. Anagnostou, E. *et al.* Metformin for Treatment of Overweight Induced by Atypical Antipsychotic  
1658 Medication in Young People With Autism Spectrum Disorder: A Randomized Clinical Trial. *JAMA*  
1659 *Psychiatry* **73**, 928 (2016).
- 1660 204. Randomized, Controlled, Crossover Trial of Methylphenidate in Pervasive Developmental Disorders  
1661 With Hyperactivity. *Arch. Gen. Psychiatry* **62**, 1266 (2005).
- 1662 205. Handen, B. L. *et al.* Atomoxetine, Parent Training, and Their Combination in Children With Autism  
1663 Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder. *J. Am. Acad. Child Adolesc.*  
1664 *Psychiatry* **54**, 905–915 (2015).
- 1665 206. Scahill, L. *et al.* Extended-Release Guanfacine for Hyperactivity in Children With Autism Spectrum  
1666 Disorder. *Am. J. Psychiatry* **172**, 1197–1206 (2015).
- 1667 207. Hollander, E. *et al.* A Double-Blind Placebo-Controlled Trial of Fluoxetine for Repetitive Behaviors  
1668 and Global Severity in Adult Autism Spectrum Disorders. *Am. J. Psychiatry* **169**, 292–299 (2012).

- 1669 208. King, B. H. *et al.* Lack of Efficacy of Citalopram in Children With Autism Spectrum Disorders and  
 1670 High Levels of Repetitive Behavior: Citalopram Ineffective in Children With Autism. *Arch. Gen.*  
 1671 *Psychiatry* **66**, 583 (2009).
- 1672 209. Anagnostou, E. *et al.* Intranasal oxytocin in the treatment of autism spectrum disorders: A review  
 1673 of literature and early safety and efficacy data in youth. *Brain Res.* **1580**, 188–198 (2014).
- 1674 210. Guastella, A. J. *et al.* The effects of a course of intranasal oxytocin on social behaviors in youth  
 1675 diagnosed with autism spectrum disorders: a randomized controlled trial. *J. Child Psychol.*  
 1676 *Psychiatry* **56**, 444–452 (2015).
- 1677 211. Parker, K. J. *et al.* A randomized placebo-controlled pilot trial shows that intranasal vasopressin  
 1678 improves social deficits in children with autism. *Sci. Transl. Med.* **11**, eaau7356 (2019).
- 1679 212. Bolognani, F. *et al.* A phase 2 clinical trial of a vasopressin V1a receptor antagonist shows improved  
 1680 adaptive behaviors in men with autism spectrum disorder. *Sci. Transl. Med.* **11**, eaat7838 (2019).
- 1681 213. Rubenstein, J. L. R. & Merzenich, M. M. Model of autism: increased ratio of excitation/inhibition in  
 1682 key neural systems. *Genes Brain Behav.* **2**, 255–267 (2003).
- 1683 214. Veenstra-VanderWeele, J. *et al.* Arbaclofen in Children and Adolescents with Autism Spectrum  
 1684 Disorder: A Randomized, Controlled, Phase 2 Trial. *Neuropsychopharmacology* **42**, 1390–1398  
 1685 (2016).
- 1686 215. Berry-Kravis, E. *et al.* Mavoglurant in fragile X syndrome: Results of two randomized, double-blind,  
 1687 placebo-controlled trials. *Sci. Transl. Med.* **8**, 321ra5–321ra5 (2016).
- 1688 216. Krueger, D. A. *et al.* Everolimus for treatment of tuberous sclerosis complex-associated  
 1689 neuropsychiatric disorders. *Ann. Clin. Transl. Neurol.* **4**, 877–887 (2017).
- 1690 217. Georgiades, S. & Kasari, C. Reframing Optimal Outcomes in Autism. *JAMA Pediatr.* **172**, 716 (2018).

- 1691 218. Bishop-Fitzpatrick, L. *et al.* Characterizing Objective Quality of Life and Normative Outcomes in  
 1692 Adults with Autism Spectrum Disorder: An Exploratory Latent Class Analysis. *J. Autism Dev. Disord.*  
 1693 **46**, 2707–2719 (2016).
- 1694 219. THE WHOQOL GROUP. Development of the World Health Organization WHOQOL-BREF Quality of  
 1695 Life Assessment. *Psychol. Med.* **28**, 551–558 (1998).
- 1696 220. Gotham, K. *et al.* Characterizing the daily life, needs, and priorities of adults with autism spectrum  
 1697 disorder from Interactive Autism Network data. *Autism* **19**, 794–804 (2015).
- 1698 221. Taylor, J. L. & Seltzer, M. M. Employment and Post-Secondary Educational Activities for Young  
 1699 Adults with Autism Spectrum Disorders During the Transition to Adulthood. *J. Autism Dev. Disord.*  
 1700 **41**, 566–574 (2010).
- 1701 222. Orsmond, G. I., Shattuck, P. T., Cooper, B. P., Sterzing, P. R. & Anderson, K. A. Social Participation  
 1702 Among Young Adults with an Autism Spectrum Disorder. *J. Autism Dev. Disord.* **43**, 2710–2719  
 1703 (2013).
- 1704 223. Henninger, N. A. & Taylor, J. L. Outcomes in adults with autism spectrum disorders: a historical  
 1705 perspective. *Autism* **17**, 103–116 (2012).
- 1706 224. Howlin, P. & Moss, P. Adults with Autism Spectrum Disorders. *Can. J. Psychiatry* **57**, 275–283  
 1707 (2012).
- 1708 225. Farley, M. A. *et al.* Twenty-year outcome for individuals with autism and average or near-average  
 1709 cognitive abilities. *Autism Res.* **2**, 109–118 (2009).
- 1710 226. Taylor, J. L., Henninger, N. A. & Mailick, M. R. Longitudinal patterns of employment and  
 1711 postsecondary education for adults with autism and average-range IQ. *Autism* **19**, 785–793 (2015).
- 1712 227. Lai, M.-C. *et al.* Quantifying and exploring camouflaging in men and women with autism. *Autism*  
 1713 **21**, 690–702 (2016).

- 1714 228. van Heijst, B. F. & Geurts, H. M. Quality of life in autism across the lifespan: A meta-analysis.  
1715 *Autism* **19**, 158–167 (2014).
- 1716 229. Moss, P., Mandy, W. & Howlin, P. Child and Adult Factors Related to Quality of Life in Adults with  
1717 Autism. *J. Autism Dev. Disord.* **47**, 1830–1837 (2017).
- 1718 230. Bishop-Fitzpatrick, L., Mazefsky, C. A. & Eack, S. M. The combined impact of social support and  
1719 perceived stress on quality of life in adults with autism spectrum disorder and without intellectual  
1720 disability. *Autism* **22**, 703–711 (2017).
- 1721 231. Kamio, Y., Inada, N. & Koyama, T. A nationwide survey on quality of life and associated factors of  
1722 adults with high-functioning autism spectrum disorders. *Autism* **17**, 15–26 (2012).
- 1723 232. Mason, D. *et al.* Predictors of quality of life for autistic adults. *Autism Res.* **11**, 1138–1147 (2018).
- 1724 233. Autistica. *Your questions shaping future autism research.*  
1725 [https://www.autistica.org.uk/downloads/files/Autism-Top-10-Your-Priorities-for-Autism-](https://www.autistica.org.uk/downloads/files/Autism-Top-10-Your-Priorities-for-Autism-Research.pdf)  
1726 [Research.pdf](https://www.autistica.org.uk/downloads/files/Autism-Top-10-Your-Priorities-for-Autism-Research.pdf). (2016).
- 1727 234. Ontario Brain Institute. *Ontario Brain Institute. Community Priorities for Research on*  
1728 *Neurodevelopmental Disorders. (2018). Available at: [http://braininstitute.ca/img/JLA-NDD-Final-](http://braininstitute.ca/img/JLA-NDD-Final-Report.pdf)*  
1729 *Report.pdf. <http://braininstitute.ca/img/JLA-NDD-Final-Report.pdf>. (2018).*
- 1730 235. den Houting, J. Neurodiversity: An insider's perspective. *Autism* **23**, 271–273 (2018).
- 1731 236. Szatmari, P. Risk and resilience in autism spectrum disorder: a missed translational opportunity?  
1732 *Dev. Med. Child Neurol.* **60**, 225–229 (2017).
- 1733 237. Markowitz, L. A. *et al.* Development and psychometric evaluation of a psychosocial quality-of-life  
1734 questionnaire for individuals with autism and related developmental disorders. *Autism* **20**, 832–  
1735 844 (2016).
- 1736 238. Ryan, S. & Cole, K. R. From Advocate to Activist? Mapping the Experiences of Mothers of Children  
1737 on the Autism Spectrum. *J. Appl. Res. Intellect. Disabil.* **22**, 43–53 (2009).

- 1738 239. McCann, D., Bull, R. & Winzenberg, T. The daily patterns of time use for parents of children with  
1739 complex needs. *J. Child Health Care* **16**, 26–52 (2012).
- 1740 240. Karst, J. S. & Van Hecke, A. V. Parent and Family Impact of Autism Spectrum Disorders: A Review  
1741 and Proposed Model for Intervention Evaluation. *Clin. Child Fam. Psychol. Rev.* **15**, 247–277 (2012).
- 1742 241. Lounds, J., Seltzer, M. M., Greenberg, J. S. & Shattuck, P. T. Transition and Change in Adolescents  
1743 and Young Adults With Autism: Longitudinal Effects on Maternal Well-Being. *Am. J. Ment. Retard.*  
1744 **112**, 401 (2007).
- 1745 242. Burke, M. & Heller, T. Individual, parent and social-environmental correlates of caregiving  
1746 experiences among parents of adults with autism spectrum disorder. *J. Intellect. Disabil. Res.* **60**,  
1747 401–411 (2016).
- 1748 243. Kim, S. H., Bal, V. H. & Lord, C. Longitudinal follow-up of academic achievement in children with  
1749 autism from age 2 to 18. *J. Child Psychol. Psychiatry* **59**, 258–267 (2017).
- 1750 244. Mendell, J. R. *et al.* Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N. Engl. J.*  
1751 *Med.* **377**, 1713–1722 (2017).
- 1752 245. Mercuri, E. *et al.* Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *N. Engl.*  
1753 *J. Med.* **378**, 625–635 (2018).
- 1754 246. Matharu, N. *et al.* CRISPR-mediated activation of a promoter or enhancer rescues obesity caused  
1755 by haploinsufficiency. *Science* **363**, eaau0629 (2019).
- 1756 247. Abudayyeh, O. O. *et al.* RNA targeting with CRISPR–Cas13. *Nature* **550**, 280–284 (2017).
- 1757 248. Lord, C., Bishop, S. & Anderson, D. Developmental trajectories as autism phenotypes. *Am. J. Med.*  
1758 *Genet. C Semin. Med. Genet.* **169**, 198–208 (2015).
- 1759 249. Amaral, D. G. *et al.* Gaps in Current Autism Research: The Thoughts of the *Autism Research*  
1760 Editorial Board and Associate Editors. *Autism Res.* **12**, 700–714 (2019).
- 1761 250. Kahn, R. S. *et al.* Schizophrenia. *Nat. Rev. Dis. Primer* **1**, (2015).



- 1762 251. Patel, V. *et al.* Addressing the burden of mental, neurological, and substance use disorders: key  
 1763 messages from Disease Control Priorities, 3rd edition. *The Lancet* **387**, 1672–1685 (2016).
- 1764 252. Franz, L., Chambers, N., von Isenburg, M. & de Vries, P. J. Autism spectrum disorder in sub-saharan  
 1765 africa: A comprehensive scoping review: Autism spectrum disorder in sub-Saharan Africa. *Autism*  
 1766 *Res.* **10**, 723–749 (2017).
- 1767 253. WHO. *Training parents to transform children's lives.*  
 1768 [https://www.who.int/mental\\_health/maternal-child/PST/en/](https://www.who.int/mental_health/maternal-child/PST/en/).
- 1769 254. Naslund, J. A. *et al.* Digital Innovations for Global Mental Health: Opportunities for Data Science,  
 1770 Task Sharing, and Early Intervention. *Curr. Treat. Options Psychiatry* (2019) doi:10.1007/s40501-  
 1771 019-00186-8.
- 1772 255. Sadowsky, J. John Donovan, Carrie Zucker. In a different key: The story of autism. *J. Hist. Behav. Sci.*  
 1773 **54**, 66–67 (2018).
- 1774 256. Rutter, M., Greenfeld, D. & Lockyer, L. A Five to Fifteen Year Follow-Up Study of Infantile Psychosis.  
 1775 *Br. J. Psychiatry* **113**, 1183–1199 (1967).
- 1776 257. B. Hermelin & N. O'Connor. *Psychological Experiments With Autistic Children.* (Pergamon Press,  
 1777 1970).
- 1778 258. Rimland, B. *Infantile Autism: the Syndrome and Its Implications for a Neural Theory of Behaviour.*  
 1779 (Meredith Publishing Compan, 1964).
- 1780 259. Frith, U. Studies in pattern detection in normal and autistic children: I. Immediate recall of auditory  
 1781 sequences. *J. Abnorm. Psychol.* **76**, 413–420 (1970).
- 1782 260. Folstein, S. & Rutter, M. A Twin Study of Individuals with Infantile Autism. *Autism* 219–241 (1978)  
 1783 doi:10.1007/978-1-4684-0787-7\_15.
- 1784 261. Mundy, P., Sigman, M. & Kasari, C. A longitudinal study of joint attention and language  
 1785 development in autistic children. *J. Autism Dev. Disord.* **20**, 115–128 (1990).

- 1786 262. Pickles, A, McCauley, J.B., Pepa, L., Huerta, M. & Lord, C. The adult outcome of children referred  
1787 for autism: Typology and prediction from childhood. *J Cons and Clin Psyc* (2019).
- 1788 263. Schopler, E. & Reichler, R. J. Parents as cotherapists in the treatment of psychotic children. *J.*  
1789 *Autism Child. Schizophr.* **1**, 87–102 (1971).
- 1790 264. Sinclair, J. *Don't mourn for us*. [http://www.autreat.com/dont\\_mourn.html](http://www.autreat.com/dont_mourn.html). (1993).
- 1791 265. Wing, L. & Gould, J. Severe impairments of social interaction and associated abnormalities in  
1792 children: Epidemiology and classification. *J. Autism Dev. Disord.* **9**, 11–29 (1979).
- 1793 266. Chawner, S. *et al.* A GENETIC FIRST APPROACH TO DISSECTING THE HETEROGENEITY OF AUTISM:  
1794 PHENOTYPIC COMPARISON OF AUTISM RISK COPY NUMBER VARIANTS. *Eur.*  
1795 *Neuropsychopharmacol.* **29**, S783–S784 (2019).
- 1796 267. Modabbernia, A., Mollon, J., Boffetta, P. & Reichenberg, A. Impaired Gas Exchange at Birth and  
1797 Risk of Intellectual Disability and Autism: A Meta-analysis. *J. Autism Dev. Disord.* **46**, 1847–1859  
1798 (2016).
- 1799 268. Christensen, J. *et al.* Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and  
1800 Childhood Autism. *JAMA* **309**, 1696 (2013).
- 1801 269. Xie, F., Peltier, M. & Getahun, D. Is the Risk of Autism in Younger Siblings of Affected Children  
1802 Moderated by Sex, Race/Ethnicity, or Gestational Age? *J. Dev. Behav. Pediatr.* **37**, 603–609 (2016).
- 1803 270. Guy, A. *et al.* Infants Born Late/Moderately Preterm Are at Increased Risk for a Positive Autism  
1804 Screen at 2 Years of Age. *J. Pediatr.* **166**, 269-275.e3 (2015).
- 1805 271. Schendel, D. & Bhasin, T. K. Birth Weight and Gestational Age Characteristics of Children With  
1806 Autism, Including a Comparison With Other Developmental Disabilities. *PEDIATRICS* **121**, 1155–  
1807 1164 (2008).

- 1808 272. Windham, G. C. *et al.* Maternal Pre-pregnancy Body Mass Index and Gestational Weight Gain in  
 1809 Relation to Autism Spectrum Disorder and other Developmental Disorders in Offspring. *Autism*  
 1810 *Res.* **12**, 316–327 (2018).
- 1811 273. Schmidt, R. J. *et al.* Maternal periconceptional folic acid intake and risk of autism spectrum  
 1812 disorders and developmental delay in the CHARGE (Childhood Autism Risks from Genetics and  
 1813 Environment) case-control study. *Am. J. Clin. Nutr.* **96**, 80–89 (2012).
- 1814 274. Conde-Agudelo, A., Rosas-Bermudez, A. & Norton, M. H. Birth Spacing and Risk of Autism and  
 1815 Other Neurodevelopmental Disabilities: A Systematic Review. *PEDIATRICS* **137**, e20153482–  
 1816 e20153482 (2016).
- 1817 275. Lyall, K. *et al.* The Changing Epidemiology of Autism Spectrum Disorders. *Annu. Rev. Public Health*  
 1818 **38**, 81–102 (2017).
- 1819 276. Cheslack-Postava, K., Liu, K. & Bearman, P. S. Closely Spaced Pregnancies Are Associated With  
 1820 Increased Odds of Autism in California Sibling Births. *PEDIATRICS* **127**, 246–253 (2011).
- 1821 277. Conti, E., Mazzotti, S., Calderoni, S., Saviozzi, I. & Guzzetta, A. Are children born after assisted  
 1822 reproductive technology at increased risk of autism spectrum disorders? A systematic review.  
 1823 *Hum. Reprod.* **28**, 3316–3327 (2013).
- 1824 278. Lehti, V. *et al.* Autism spectrum disorders in IVF children: a national case-control study in Finland.  
 1825 *Hum. Reprod.* **28**, 812–818 (2013).
- 1826 279. Rossignol, D. A., Genuis, S. J. & Frye, R. E. Environmental toxicants and autism spectrum disorders:  
 1827 a systematic review. *Transl. Psychiatry* **4**, e360–e360 (2014).
- 1828 280. Curran, E. A. *et al.* Research Review: Birth by caesarean section and development of autism  
 1829 spectrum disorder and attention-deficit/hyperactivity disorder: a systematic review and meta-  
 1830 analysis. *J. Child Psychol. Psychiatry* **56**, 500–508 (2014).

- 1831 281. Chandler, S., Howlin, P., Simonoff, E., Kennedy, J. & Baird, G. Comparison of parental estimate of  
 1832 developmental age with measured IQ in children with neurodevelopmental disorders. *Child Care*  
 1833 *Health Dev.* **42**, 486–493 (2016).
- 1834 282. Charman, T. *et al.* IQ in children with autism spectrum disorders: data from the Special Needs and  
 1835 Autism Project (SNAP). *Psychol. Med.* **41**, 619–627 (2010).
- 1836 283. Sparrow, S. S., Cicchetti, D. & Balla, D. A. Vineland Adaptive Behavior Scales, Second Edition. (2005)  
 1837 doi:10.1037/t15164-000.
- 1838 284. Jones, R. M., Pickles, A. & Lord, C. Evaluating the quality of peer interactions in children and  
 1839 adolescents with autism with the Penn Interactive Peer Play Scale (PIPPS). *Mol. Autism* **8**, (2017).
- 1840 285. Lord, C., Elsabbagh, M., Baird, G. & Veenstra-Vanderweele, J. Autism spectrum disorder. *The*  
 1841 *Lancet* **392**, 508–520 (2018).
- 1842 286. Duncan, A. W. & Bishop, S. L. Understanding the gap between cognitive abilities and daily living  
 1843 skills in adolescents with autism spectrum disorders with average intelligence. *Autism* **19**, 64–72  
 1844 (2013).
- 1845